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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A01N 25/02, 25/02, 37/02, 37/06

A2

(11) International Publication Number: **WO 96/29867**

(43) International Publication Date: 3 October 1996 (03.10.96)

(21) International Application Number: PCT/US96/04258

(22) International Filing Date: 28 March 1996 (28.03.96)

(30) Priority Data:
08/412,327 31 March 1995 (31.03.95) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/412,327 (CIP)
Filed on 31 March 1995 (31.03.95)

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(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: FAST ACTING AND PERSISTENT TOPICAL ANTISEPTIC

(57) Abstract

Stable antiseptic compositions having both a quick-kill of microorganisms with a substantial reduction in number, and a profound persistent effect over a broad spectrum of microorganisms, including but not limited to bacteria, yeasts, molds, and viruses, without significant irritation of the tissue to which they are applied are disclosed. The quick-kill component of the present invention comprises one or more alcohols, lipids, preservatives or microbicidal nitrogen containing compounds. The persistent component of the present invention comprises one or more lipids, preservatives, or microbicidal nitrogen containing compounds which preferably bind to either or both of the skin surface and intracellular structures within the epidermis. Additional components include antioxidants, ethoxylated cetyl and stearyl alcohols, coloring and texturing compounds. Preferred solutions comprise an alcohol such as 70 % n-propanol or ethanol and bispyrithiones and further include fatty acids and fatty acid esters.

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FAST ACTING AND PERSISTENT TOPICAL ANTISEPTIC

TECHNICAL FIELD

This invention relates to topical antiseptic compositions.

BACKGROUND OF THE INVENTION

Humans have recognized the need for antiseptics since ancient times. An antiseptic is an agent used on or in living tissue to inhibit the growth and activity of microorganisms or to destroy them. Even though the early humans did not understand the reasons why infection occurred, they did understand that certain compositions reduced the likelihood of infection and, therefore, increased the likelihood that a patient to whom the composition was applied was going to survive an injury or infection. The compositions that were most effective were naturally occurring antiseptics. In the late 1800's, scientists such as Lister began to recognize the cause of infection and that treatment of a wound with an antiseptic would significantly improve the chance of survival of the patient. Antiseptics also made possible the removal of microorganisms from surgeon's skin prior to operations which could have otherwise infected the patient, potentially leading to death.

Currently, there are several conventional antiseptics which are effective against microorganisms which cause mammalian infection, approved for use by the Food and Drug Administration, and commonly used in hospitals. These conventional antiseptics provide varying degrees of antimicrobial activity. Antimicrobial activity is classified as high, i.e., killing vegetative bacteria, acid-fast bacteria, bacterial spores, fungi, lipid and medium-sized viruses, and nonlipid and small viruses; intermediate, i.e., killing all the above except for possibly

bacterial spores and nonlipid and small viruses; and low, i.e., killing vegetative bacteria, lipid and medium-sized viruses and possibly fungi but ineffective against acid-fast bacteria, bacterial spores, and nonlipid and small viruses. Alcohols such as ethanol and isopropanol at 70% (v/v) provide intermediate antimicrobial action. Iodophor in concentrations of 1-2 milligram per liter with 1%-2% available iodine are considered intermediate to low antimicrobial antiseptics. Chlorhexidine (0.75%-4.0%), hexachlorophene (1%-3%), parachlorometaxylenol (0.5%-4%), and mercurial compounds (0.1%-0.2%) are antiseptics of low antimicrobial activity.

The degree of antimicrobial action for a given antiseptic is influenced by several factors. As indicated by the classification given above, the type of microorganism greatly affects microbicidal level, with spore-formers and certain viruses such as nonlipid and small viruses being the most difficult to kill. Under a given set of circumstances, the higher the level of microbial contamination, the longer the exposure to the antiseptic is required for microbicidal activity. The ability of the antiseptic to penetrate to all contaminated surfaces also affects the degree of killing.

While exposure of microorganisms maintained on a smooth surface or in a liquid solution to many conventional antiseptics (such as alcohols) will eventually kill virtually all of the microorganisms, the skin presents some unusual problems. Even though conventional antiseptics are effective at killing

a vast majority of the microorganisms present on the surface, there is a continuing problem with a small percentage of the microorganisms remaining viable in the superficial and deeper layers of the skin. For example, if skin originally contains one million bacteria per square centimeter and there is a four log reduction in the number of bacteria subsequent to application of the antiseptic, there remains approximately one hundred bacteria still viable in the superficial and deeper layers of the skin. Skin bacteria have been described as "transients" and "residents". The transient bacteria lie free on the skin or are loosely attached. The transient bacteria are removed rather easily. The resident bacteria are very difficult, if not impossible, to remove. These bacteria may be partially hidden from antiseptics; in particular, the skin has numerous sweat ducts and hair follicles on a microscopic level that allows microorganisms to be beneath the exposed surface and potentially miss being killed by antiseptic treatments. But more importantly, the resident bacteria are within the stratum corneum and are not killed with conventional antiseptics.

The quality of persistence, sometimes also referred to as residual activity or substantivity, refers to the ability of an antiseptic to continue to kill once it is applied. According to the U.S. Food and Drug Administration (FDA), "a property [of an antiseptic] such as persistence, which acts to prevent the growth or establishment of transient mircoorganisms as part of the normal baseline or resident flora, would

be an added benefit." *Federal Register* 59:31407 (June 17,1994). Most conventional antiseptics have a relatively short persistence, such that within a few hours the quantity of microorganisms on tissue will return to the original numbers. For example, if a conventional alcohol antiseptic is utilized on the skin, the number of microorganisms per square centimeter are effectively back to their original level after approximately three hours. Furthermore, during that three hour period the bacterial colonies are expanding significantly with each passing hour, that is, bacteria are multiplying during that time and do not just rebound to normal levels at the end of the three hour time period.

Chlorhexidine gluconate, reported to be the best persistent antiseptic available, has demonstrated antiseptic activity for about six hours. Larson, E., "APIC guidelines for infection control practice," *American J Infection Control* 16:253-66 (1988).

As it is desirable to maintain medical procedures as free of microorganisms as possible, it is desirable to have persistence associated with an antiseptic that both maintains the microorganism count at as low a level as possible and for as long as possible. This is especially true where there is an open wound, or where a patient is being operated upon for many hours and it is important to minimize the microorganism count of both the operative site and the hands of the surgeon for as long as possible. Moreover, this is also true around a chronic indwelling device. In such cases, if

the microorganism level returns to greater than fifteen colony forming units per square centimeter on the skin of the patient, the likelihood is that the site of the wound, procedure, device, or operation will also become infected.

While certain conventional antiseptics are highly effective against microorganisms causing mammalian infection, they do not provide in a single composition a very broad spectrum, quick-acting and persistent antiseptic that kills as many different microorganisms as possible, especially those that are most likely to cause serious injury to humans due to infection. Currently available antiseptics still often leave a variety of microorganisms in the treated tissue which may lead to infection with a significant increase in morbidity and mortality. Consequently, there has been a continuing need to improve antiseptics which will kill as many microorganisms as possible on the surface and in the epidermis of the skin in a short period of time and, especially, produce persistence to maintain such kill for an extended period of time.

Novel antiseptics have now been found which are very broad spectrum having antimicrobial activity against microorganisms such as but not limited to vegetative bacteria, yeasts, molds, and viruses, quick-acting and persistent antiseptics, which are non-irritating, have reasonably pleasant characteristics associated with the senses of the persons using the antiseptic such as having a pleasant smell, and have a good tactile feel when applied to the skin. These antiseptics are easily modified to be used over a broad

range of uses such as a topical antiseptic applied to the skin of humans or other mammals; a skin preparation antiseptic for use prior to medical operations; a hand wash for doctors and other medical practitioners; an antiseptic at medical appliance invasive sites such as locations where needles or tubes are placed within the skin or open wounds; a microorganism barrier or an antiseptic within various orifices such as the ear or vagina; an antiseptic to be utilized on sensitive membranes such as mucous membranes, eyes or genitalia; an antiseptic to be used in the treatment of inflammatory dermatoses, e.g., acne, athlete's foot, psoriasis and fungal infections; an antiseptic treatment for use on animals to prevent infection, e.g., as a treatment against bovine mastitis; and an antiseptic to be applied to the surface of devices which are subsequently applied to skin such as gloves, drapes, or tape.

SUMMARY OF THE INVENTION

According to the invention, new antiseptic formulations for topical application are provided as stable, non-irritating solutions or emulsions effective for quickly killing microorganisms present in a treated area and for providing a continued killing or inhibitory effect for greater than six hours. These formulations each contain at least one broad spectrum, fast-acting antimicrobial agent effective for decreasing the number of microorganisms on the treated skin in combination with at least one persistent agent effective for prolonging the antimicrobial activity of said antimicrobial agent.

The persistent agent may be a lipid such as fatty acids, fatty acid esters, phospholipids, glycosphingolipids, and mixtures thereof. In one aspect of the present invention, the lipid is a fatty acid, preferably having a chain length of from 2 to about 20 carbons, and most preferable, linoleic or linolenic acid. In another aspect, the lipid is a fatty acid ester, preferably having a chain length of from 2 to about 24 carbons, and most preferable, glycerol monolaurate.

The persistent agent may be a nitrogen compound such as pyridine-containing compounds, alkyl amines, arylalkyl amines, quaternary ammonium compounds, biguanides, bisbiguanides, amine oxides, quinolines, nitrogen-containing antibiotics, and mixtures thereof. In one aspect of the present invention, the persistent agent is a bispyrithione compound.

The persistent agent may be a preservative such as phenolic acids and salts; acetic acid and salts; sorbic acid and salts; propionic acid and salts; lactic acid and salts; boric acid and salts; dehydroacetic acid; sulphurous and vanillic acids; phenol; cresol; chlorocresol; o-phenylphenol; chlorothymol; propyl and butyl esters of parahydroxy-benzoic acid; benzyl-p-hydroxy benzoates; thimerosal; phenylmercuric acetate; phenylmercuric nitrate; nitromersol; sodium ethylmercurithiosalicylate; benzyl alcohol; beta-phenylethyl alcohol; phenylethyl alcohol; phenoxy-2-ethanol; imidazolidinyl urea; diazolidinyl urea; p-cymene; linalool; geraniol; nerol; thymol; carvacrol; eugenol; isoeugenol; safrole; benzaldehyde; cumic aldehyde; cinnamic aldehyde; salicylaldehyde; pulegone; thujone; ascaridole; chlorhexidine; chloroform; bronopol; glydant; mixtures of 5-chloro-2-methyl-3-(2H)isothiazolone and 2-methyl-3-(2H)isothiazolone, and mixtures thereof.

The antiseptic formulation of the present invention may also contain a penetration controlling agent such as unsaturated long-chain fatty acids, esters of fatty acids, propylene glycol, medium-chain saturated fatty acids, medium-chain alcohols (C8 through C14), amine oxides, mineral oil, petrolatum, cetyl alcohol, stearyl alcohol, polymers of linoleic acid, and mixtures thereof.

In one embodiment of the present invention, the topical antiseptic formulation comprises an antimicrobial alcohol, glycol or combination thereof, a persistent nitrogen compound, and water. In a preferred

aspect of the invention, the alcohol or glycol has less than 14 carbon atoms. Preferred alcohols are n-propanol, isopropanol, ethanol, and phenylethyl alcohol. A preferred glycol is propylene glycol. The nitrogen compound must have at least one nitrogen atom which is free from steric hindrance and able to bind irreversibly to the surface or intracellular structures of the treated area. Preferred nitrogen compounds include amine oxides, biguanides or bisbiguanides, quaternary ammonium compounds, pyridine compounds, bispyrithiones, quinoline compounds, nitrogen-containing antibiotics, and dodecylammonium salts. Most preferred is a bispyrithione compound at from about 0.0005% to about 10% (w/v). Optionally, the antiseptic formulation may contain a lipid such as fatty acids, fatty acid esters or mixtures thereof; a preservative; an emulsifying agent; 2-deoxy-D-glucose; hyaluronic acid; glycyrrhetinic acid; or an iodophor. A preferred embodiment comprises from about 30% to about 98% (v/v) alcohol, glycol, or combination thereof, from about 0.0001% to about 15% (w/v) nitrogen compound, and from about 1% to about 69% (v/v) water. A more preferred embodiment comprises from about 40% to about 95% (v/v) alcohol, glycol, or combination thereof, from about 0.0001% to about 12% (w/v) nitrogen compound, and from about 26% to about 60% (v/v) water. A most preferred embodiment comprises about 70% (v/v) alcohol, glycol, or combination thereof, from about 0.0001% to about 10% (w/v) nitrogen compound, and from about 7.5% to about 30% (v/v) water. The preferred pH

range is between 2 and 5; more preferred, between 3 and 4, and most preferred, less than 7.

In another embodiment of the present invention, the topical antiseptic formulation comprises a lipid, a nitrogen compound, and water. Preferred lipids include fatty acids, fatty acid esters, phospholipids, glycosphingolipids, and mixtures thereof. Preferred fatty acids have a chain length of from 2 to about 20 carbons, and most preferably are linoleic or linolenic acid. Preferred fatty acid esters have a chain length of from 2 to about 24 carbons, and preferably is glycerol monolaurate. Preferable nitrogen compounds are the same as the ones in the embodiment described above. Optionally, the antiseptic formulation may contain a glycol, preferably propylene glycol; a preservative; an emulsifying agent; zinc sulfate, preferably from about 0.1% to about 5% (w/v); 2-deoxy-D-glucose; hyaluronic acid; glycyrrhetinic acid; or an iodophor.

DETAILED DESCRIPTION

The present invention is directed to a topical antiseptic that advantageously provides both a very fast acting antimicrobial action, or quick kill, of existing microorganisms on the surface of living tissue and is persistent in preventing the return of microorganisms to the treated surface. Fast acting antimicrobials provide profound, immediate bactericidal properties indicated by a significant log drop in the number of organisms obtained by culturing the application site within a few minutes post-application when compared to microbial counts taken prior to application of the antimicrobial.

The property of persistence is provided by a composition which is bound by physiochemical forces to cause the antimicrobial composition to establish a reservoir in and/or on the stratum corneum. This reservoir exerts an antimicrobial effect for several hours or days beyond the last application of the antimicrobial composition, because the antimicrobial composition is retained in the stratum corneum until the cells to which the antimicrobial composition is fixed are shed in the normal process of desquamation. The degree of persistence is measured by the length of time required for microflora to be fully restored to baseline counts following use or repeated use of the antimicrobial composition.

In addition to the quick kill components and persistent components of the present invention, the antiseptic compositions may also contain penetration enhancing components, chelating agent components,

antioxidants, emulsifiers, colorings, texturings, and over-the counter (OTC) treatments.

It is preferred to have an antiseptic that not only quickly kills microorganisms with a high log ratio kill on contact with the skin, but also has the ability to: 1) penetrate throughout the levels of the skin where microorganisms reside without irritating or doing substantial harm to the treated area, 2) bind to lipids or proteins in the intercellular layers of the epidermis to produce a prolonged kill or persistence, and 3) bind to lipids or proteins on the surface of the skin so as to have a prolonged or persistent kill where organisms are killed as they attempt to recolonize the skin surface from their resident sources. Persistence in antimicrobials is especially important in adolescents and adults. In neo-nates where the skin is only a few cell layers thick, with less resident flora, persistence can be achieved with less penetrating ability.

Antiseptics of the present invention are useful over a wide range of antiseptic uses and may be easily modified for efficacy requiring specific characteristics. For example, these antiseptics can be utilized as an antiseptic skin preparation for a patient undergoing an operation; a pre-operative scrub for the hands of physicians or other medical technicians; a health care personnel hand wash; a routine hand wash; an antiseptic around invasive sites for medical appliances such as needles and catheters; a treatment for inflammatory dermatoses such as acne and topical fungal infections; an antiseptic for use in

sensitive areas such as mucous membranes, eyes, ears, genitalia, and vagina; and as an antiseptic applicable to ways in which other conventional antiseptics and antimicrobials are utilized.

In particular, the antiseptic compositions of the present invention comprise a quick-kill component(s) and a persistent component(s). It is especially desirable that these two components along with other ingredients of the invention render the tissue treated by the antiseptic hydrophobic and lipophilic. The persistent component(s) binds to either the skin surface and/or intercellular structures within the epidermis.

The quick-kill component of the antiseptic composition of the present invention preferably comprises an alcohol which is microbicidal, relatively inexpensive, and relatively nontoxic with topical application. Alcohols also tend to have a cleansing action and evaporate rapidly, helping to desiccate the skin and to produce an environment that is incompatible with microorganism survival.

The alcohol of the present invention may be of high, medium, or low carbon chain length and is preferably at least partially miscible with water. Most preferably, in some applications, the alcohol selected will be fully miscible with water. Medium-chain alcohols may be selected when microbicidal efficacy is a more important factor than full miscibility. Most of the alcohols are colorless but can be dyed where color is desirable.

Typical alcohols usable as a quick-kill component of the present invention are aliphatic alcohols, including methyl, ethyl, isopropyl, propyl, butyl, and amyl alcohol. The bactericidal action of the alcohols increases with the molecular weight of the alcohol except for the tertiary alcohols. The propyl alcohols, including n-propanol and isopropyl alcohol, are, in general, the highest molecular weight aliphatic alcohols that are fully miscible with water in all proportions and are commonly used as antiseptics.

N-propanol is the preferred quick-kill agent in accordance with the present invention as it is the strongest bactericide against most microorganisms of interest as well as the longest carbon chain length alcohol which is fully miscible with water in all proportions, compatible with topical application to the skin, and commonly available. N-propanol may be used by itself as a quick-kill component or in combination with other alcohols and other quick-kill agents. For example, other alcohols that are highly suitable for the quick-kill component include ethyl alcohol or isopropyl alcohol.

In the present invention, higher chain length alcohols may also be used, especially in mixtures. For example, amyl alcohol has very good microbicidal activity and slower evaporation. Alcohols such as n-decanol, a penetration enhancing agent, may also be useful when blended with other lower molecular weight alcohols.

While alcohols are fairly effective at killing microorganisms at neutral pH, this effectiveness

increases dramatically at a lower pH. Consequently, it is desirable that compositions in which alcohols are the sole quick kill component should utilize the following pH levels: for intact skin, pH 4 or less, preferably from about 2 to about 3.5; for vagina, pH of about 4.5; for the ear canal, pH of about 4.5; for the external ear, pH of about 3.5 to about 4.5; for the eye, pH of about 7.2 to about 7.8, preferably at about 7.5; and for mucous membranes, pH of about 3.7 to about 5.5. Other ingredients added to the composition of the present invention may modify the pH and, therefore, the pH of the overall composition should be adjusted subsequent to addition of all of the components. For example, the solution may be adjusted with a phosphoric acid/monobasic sodium phosphate buffer, glacial acetic acid/sodium acetate buffer, citric acid/sodium citrate buffer, or combinations of organophosphonates such as Dequest 2010, 2060, and 2016 (Monsanto Company, St. Louis, MO).

The effectiveness of the quick-kill component is also concentration-related. In particular, most alcohols acting against common, non-spore forming bacteria under moist conditions will be ineffective against many microorganisms at concentrations less than 30% volume/volume (v/v) but fairly effective above 40% (v/v) with a time exposure of one minute. However, under either wet or dry conditions, alcohol concentrations of 60% to 70% (v/v) are most effective against microorganisms of interest. Alcohol concentrations of 100% are not useful in the present invention as some water needs to be present in the

alcohol for it to be bactericidal. In the antiseptic compositions of the present invention, most alcohols preferably are utilized in concentrations ranging of from about 50% to about 70% (v/v) with the latter being the most preferred. For example, 70% (v/v) N-propanol is the most preferred quick-kill agent.

In accordance with the present invention, aromatic alcohols may also be utilized advantageously in conjunction with other aliphatic alcohols such as n-propanol. The preferred aromatic alcohols include phenylethyl alcohol, benzyl alcohol, and phenoxyethyl alcohol.

For use in conjunction with portions of the body that are sensitive to some of the aliphatic or aromatic alcohols, e.g, on mucous membranes or the genitalia, it is preferred that the quick-kill component and solvent for other ingredients be propylene glycol or 1,4-butene diol in concentrations greater than 30%, raising the pH to about 4 to about 5. Propylene glycol not only provides a quick-kill effect, but also has the added advantages of being a penetration enhancing agent, slowing the evaporation of the other components of the composition (especially light alcohols) and having an emollient effect when used on the skin.

Additional components may be used in conjunction with or as a replacement for the alcohols as the quick-kill component. Many of the previously utilized or conventional antiseptics fit this criteria, including chlorhexidine gluconate, iodine, iodophors, phenol derivatives, quaternary ammonium compounds, certain

heavy metals, para-chloro-meta-xylenol (PCMX), and 5-chloro-2-(2,4-dichloro-phenoxy)phenol (Triclosan).

Some of the most effective known antiseptic compositions include chlorhexidine gluconate in combination with alcohols such as isopropyl alcohol, ethyl alcohol, n-propanol or their mixtures. It is possible in accordance with the present invention to utilize chlorhexidine in conjunction with an alcohol as the quick-kill component; however, the pH of the composition must then be maintained above what is otherwise desirable for the composition. In particular, the composition containing chlorhexidine gluconate must be within the pH range of 5 to 7 in order to remain stable.

In conjunction with the quick kill component, the present invention also comprises a persistent component. The main purpose for the inclusion of a persistent component is that the substantivity or residual activity of the quick-kill components, especially the alcohols, is relatively short lived. Most of the currently used antiseptics have a residual activity of one to six hours. For example, a combination of alcohol and chlorhexidine gluconate with multiple applications has been reported to have residual microbicidal activity for up to six hours. Larson, E.L., "APIC guideline for use of Topical antimicrobial agents," *Am J Infect Control* 22:25A-47A (1994). In order to achieve persistence in excess of six hours, especially up to twenty-four hours or beyond, it is necessary to incorporate one or more of the persistent components of the present invention.

Preferable persistent components are lipid or lipid-like materials including: fatty acids; fatty acid dimers, trimers, or tetramer acids; fatty acid esters; phospholipids and glycosphingolipids. It is noted that the preferred lipid materials of the present invention for use as the persistent component are naturally occurring materials within the human: free fatty acids, phospholipids, and glycosphingolipids. These lipid components are also antimicrobial, thus providing additional quick-kill activity in conjunction with the quick-kill component.

In particular, the lipid component is preferably a free fatty acid. The free fatty acid may be saturated or unsaturated, straight or branched with chain lengths of two to thirty carbons. As used herein short-chain length fatty acids will have between one and five carbon atoms; medium-chain fatty acids, between six and twelve carbon atoms; long-chain fatty acids, between thirteen and eighteen carbon atoms; and very long-chain fatty acids, greater than eighteen carbons atoms. Because of their special effectiveness against different ranges of microorganisms and penetrating ability, many of the compositions of the present invention will utilize more than one range of free fatty acids, or their polymers, i.e., dimers, trimers, and tetrameres.

A preferred medium-chain saturated fatty acids is C12, or lauric acid. For the long-chain fatty acids, linolenic and linoleic acids are preferred for non-inflamed skin, while linoleic acid or gamma-dihomolinolenic acid are preferred for inflamed skin.

The saturated or unsaturated free fatty acids above C16 are generally preferred over the lower chain fatty acids because they tend to be less irritating to the skin. The free fatty acids are also suitable for use on the skin as they are a natural component of the body. While purified, single component free fatty acids, e.g., 100 % pure linolenic or linoleic acids, are comparatively very expensive to obtain, saturated and unsaturated fatty acid mixtures are readily available as hydrolysates of various oils such as linseed oil, coconut oil, corn oil, soybean oil, evening primrose oil, borage oil, wheat germ oil and the like. These oils are often a very good source of linolenic and linoleic acids.

As antimicrobials, certain fatty acids are especially effective against certain types of microorganisms. Short-chain saturated free fatty acids are especially effective in killing gram-negative bacteria. Medium-chain free fatty acids are most effective against yeasts at neutral pH and aiding penetration into the stratum corneum. Long-chain unsaturated fatty acid tends to have the greatest activity against gram-positive microorganisms, with the activity typically increasing as the number of double bonds within the unsaturated fatty acids increases. The most microbicidal monosaturated fatty acid is C16:1, and the most active polyunsaturated fatty acid is C18:2. Typically, the cis form of the fatty acid is preferred over the trans. It is also noted that acetylenic fatty acids have a higher activity against fungus than ethylenic fatty acids.

The long chain unsaturated free fatty acids such as linoleic acid (C18:2) provided in commercial products such as Emery 305 or Emery 315 (Henkle Corporation, Emery Group, Cincinnati, OH) and oils supplying linoleic acid, such as safflower oil, sunflower oil, wheat germ oil, evening primrose oil, or sesame seed oil, are preferred antimicrobials. Also, linoleic acid is found to function as a false substrate for arachidonic acid metabolism which normally results in inflammation. Examples where linoleic acid could function both as an antimicrobial and an anti-inflammatory agent would include acne, psoriasis, athlete's foot, atopic dermatitis and eczema. Polymers of linoleic acid, i.e., dimer, trimer, and polybasic acids could be incorporated to function as an antimicrobial agent and reduce irritation from various detergents or irritants. Linolenic acid (C 18:3) should only be used on intact, non-inflamed skin as this compound is very pro-inflammatory if used on inflamed skin. This is because linolenic acid from the Omega 3 series can be elongated by skin enzymes to pro-inflammatory products, e.g., arachidonic acid. Gamma-dihomo-linolenic acid (C20:3) from the Omega 6 fatty acids are metabolized by the skin to anti-inflammatory prostaglandin E-1. So the selection of the long chain unsaturated fatty acid depends on whether one is treating inflamed or non-inflamed skin.

Fatty acid esters of the present invention may be: 1) monoglycerol esters of fatty acids with carbon chain lengths from two to twenty-four; 2) methyl esters of fatty acids including alpha-hydroxymethyl esters; 3)

poly (tri-, hexa- and deca-) glycerol esters with carbon chain lengths from two to twenty-four, saturated or unsaturated, straight or branched; 4) sucrose esters of fatty acids including cis and trans isomers; or (5) di- and triglycerol esters with carbon chain lengths from two to twenty-four.

Although fatty acids that are esterified to monohydric alcohols are fairly inactive as microbicides in the present invention, certain fatty acids esterified to a polyhydric alcohols typically become more active. For example, lauric acid is perhaps a preferred fatty acid from a point of view of activity of medium-chained fatty acids; however, it is noted that it can cause irritation of the skin on repeated use when used in conjunction with alcohols, for example a 70% solution of n-propanol. When lauric acid is esterified to glycerol to form a monoester therewith, but not the di- or tri- esters, it has been found to have a high activity. Functioning, as an emollient, it retards the evaporation of alcohol and is also no longer irritating to the skin. For this reason the glycerol monolaurate is one preferred persistent component either utilized by itself or in conjunction with other compositions as a synergistic quick-kill and/or persistent component.

As seen with the quick kill alcohols, the fatty acids and fatty acid esters also tend to increase in antimicrobial activity as the pH of the composition decreases. Typically, as the pH of a solution containing the fatty acids decreases and/or as the chain length of the fatty acid increases, the

microbicidal activity of the fatty acid also increases. Long-chain unsaturated fatty acids are more effective against gram-positive microorganisms at a neutral pH. However, long-chain unsaturated fatty acids as well as the medium-chain saturated fatty acids and the lauric acid ester of glycerol are active against gram-negative bacteria as the composition becomes more acidic, especially in the presence of a calcium and magnesium chelator. Preferred calcium and magnesium chelators are citric acid, phosphoric acid, phosphonic acids and polyphosphoric acids at an acid pH, or sodium hexametaphosphate, sodium tripolyphosphate or EDTA at neutral pH.

For the best activity, it is necessary for the fatty acids to be free fatty acids in solution. An anionic, cationic or non-ionic surfactant may impair the free fatty acid performance in microbicidal activity. When free fatty acids are used as the persistent, penetrating, or quick-kill component in the present invention, the alcohols or glycols are preferred as a synergistic quick-kill ingredient, and the alcohols or glycols typically are good solvents for the free fatty acids. It is possible to add iodine to this solution to further improve the bactericidal effects of the solution; however, when unsaturated fatty acids are utilized, it is necessary to add excess iodine and iodide to account for the halogenation of the unsaturated fatty acids sites by the iodine. This is accomplished by the addition of iodide in a ratio of at least two equivalent weights of iodide to iodine.

The preferred quick-kill and persistent lipid components of the present invention for intact skin include medium-chain saturated fatty acid monoesters, long-chain unsaturated free fatty acids, and long-chain unsaturated fatty acid polymers. The preferred range of the medium-chain fatty acid esters is from about 0.001% to 7% by weight; and more preferred, from about 1% to about 3% by weight. The preferred medium-chain fatty acid monoester is glycerol monolaurate (Lauricidin). The range for the unsaturated fatty acid is from about 0.0001% to about 30% by weight, the preferred range is from about 0.01% to about 10% by weight, and the most preferred range is from about 1% to about 50% by weight.

The preferred lipid components of the present invention for application to the eyes, ears, and vagina would include the short-chain free fatty acids in combination with the medium-chain fatty acids and long-chain fatty acids. The desirable range of the short-chain fatty acids is from 0.01% to 15% by weight and preferably from 0.1% to 10% by weight.

Other preferred lipids of the present invention are phospholipids such as lysolecithin, phosphatidylcholine, phosphatidyl-ethanolamine, phosphatidylserine, phosphatidylinositol, and phosphatidyl-N-acylethanolamine. It is also foreseen that glycosphingolipids, especially those enriched in n-acyl-alpha-hydroxyacids could be used. Other components with long alkyl groups with a lipophilic, hydrophobic end are foreseen as useable. This would include long-chain alcohols, saturated or unsaturated,

straight or branched; medium to long-chain aldehydes, saturated or unsaturated; and saturated or unsaturated alkyl amides.

Other persistent components may be added to the antiseptic composition of the present invention: oils, preservatives, and/or nitrogen compounds including pyridinethiones.

Oils, with their inherent lipophilic, hydrophobic character could function as a lipid persistent component in the present invention. This would include: safflower oil, sesame seed oil, wheat germ oil, evening primrose, soybean oil, canola oil, tea tree oil (Lelaleuca alternifolia), eugenol, isoeugenol, thyme (White and Red), cinnamon, bay oil, linseed oil, and borage oil.

Certain preservatives may be added to the antiseptic composition as highly effective quick-kill and/or persistent components. These include preservatives that are conventionally utilized in the cosmetics industry: 1) acids and phenolics such as benzoic acid and salts, acetic acid and salts, sorbic acid and salts, propionic acid and salts, lactic acid and salts, boric acid and salts, dehydroacetic acid, sulphurous and vanillic acids, phenol, cresol, chlorocresol, o-phenylphenol, chlorothymol, parabens (alkyl esters of parahydroxy-benzoic acid such as methyl-, ethyl-, propyl-, butyl- and benzyl-p-hydroxy benzoates); 2) mercurials such as thimerosal, phenylmercuric acetate and nitrate, nitromersol, and sodium ethylmercurithiosalicylate; 3) aromatic alcohols such as benzyl alcohol, beta-phenylethyl

alcohol, phenylethyl alcohol (especially effective against gram-negative organisms, e.g., Pseudomonas), and phenoxy-2-ethanol; 4) imidazolidinyl urea, or Germall 115, and diazolidinyl urea, or Germall II (Sutton Laboratories, Inc., Chatham, NJ); 5) oils such as p-cymene, linalool, geraniol, nerol, thymol, carvacrol, eugenol, isoeugenol, safrole, benzaldehyde, cumic aldehyde, cinnamic aldehyde, salicylaldehyde, pulegone, thujone, ascaridole, and cineol; 6) miscellaneous agents such as chlorhexidine, chloroform, bronopol, glydant, and a mixture of 5-chloro-2-methyl-3-(2H)isothiazolone and 2-methyl-3-(2H)isothiazolone known as Kathon CG (Rohm & Haas, Philadelphia, PA); and 7) combinations of above.

A third type quick-kill and/or persistent component which may be added to the antiseptic composition includes compounds containing nitrogen. The nitrogen is attached to chemical groups with potent antimicrobial activity and the nitrogen is not sterically hindered from being bound by physiochemical forces from establishing a reservoir in the stratum corneum. Preferably, the nitrogen compounds are soluble in sebum. Substances with NH (e.g., chlorhexidine), NH_2 (e.g., neomycin), NH_3 (e.g., dodecylammonium chloride), or NO_2 (e.g., chloromycetin) groups can readily bind to the stratum corneum.

Nitrogen is the most electronegative of all Group-V elements, leading to a high degree of reactivity on compounds containing covalently bound nitrogen. In addition, nitrogen contains five valence electrons (three unpaired, two paired), making valence states

from 5+ to 3- theoretically possible. This propensity for both covalent and ionic bonding establishes an avidity for a wide variety of interacting compounds. Such chemical diversity is the basis for the formation of antimicrobial activity by nitrogenous compounds. Also, the nitrogen is extremely important in compounds where the nitrogen remains positively charged and available for binding to negatively charged groups at the site of application. The more the nitrogen atom is free from surrounding groups that would produce steric hindrance, the greater the substantivity or persistence. The greater the number of sterically free nitrogen atoms in the nitrogenous compound, the greater the persistence. Also, alkyl or aryalkyl groups attached to the nitrogen that have bacteriocidal activity is important. Five general groups of nitrogen compounds can be added to the antiseptic composition to provide rapid bactericidal activity, persistence, penetrating and/or detergent effects.

The first group of nitrogen compounds chosen for their broad-spectrum of activity and outstanding persistence consists of pyridine compounds (Group I). Representative compounds include 2-acetyl pyridine thiosemicarbazone; 4-pyridinemethanol; pyridine oxides such as sodium 2-pyridinethiol-1-oxide, bis (2-pyridinethio) zinc-1,1'-dioxide, bispyrithiones such as zinc pyrithione and alkaline earth metal salts of bispyrithione, and N-tert-butylamino-2-pyridine-1-oxide. The pyridine oxides are substantive to hair and skin. Zinc pyrithione is not easily absorbed through intact epidermis or mucous membranes, but is soluble in

sebum and penetrates into hair follicles, thereby resisting removal by rinsing. Because of its solubility in sebum this compound is very useful in acne vulgaris, acne rosacea, and as a deodorant. It decreases the cell turnover rate in hyper proliferative dermatoses such as psoriasis and seborrhea. Because of its broad-spectrum, including fungi, this component would be useful in athlete's foot, tinea versicolor, tinea cruris, candidiasis, diaper rash, and onychomycosis.

Bispyrithione salts (also called pyridinethione salts) are highly effective as components of the present invention, including zinc and magnesium salts of bispyrithione. Unfortunately, these preferred bispyrithione salts are basically insoluble in alcohol. Consequently, it has been difficult to produce a composition using a bispyrithione in conjunction with a quick-kill component of the present invention, especially the alcohols, where the quick-kill component(s) and persistent component(s) can be incorporated in a single, stable solution.

It has also been found that magnesium pyrithione (Omadine MDS) cannot readily be used as the persistent component with the fatty acids of the present invention because an insoluble precipitate forms that reduces the activity of the free fatty acids and bispyrithione. However, magnesium pyrithione would be useful in formulas which do not incorporate fatty acids. Magnesium pyrithione would be very useful in applications for the eyes. The potent activity of this compound would allow very small concentrations to be

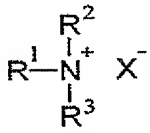
used, for example, as low as ten parts per million. Preferable concentrations would range from about 0.0001% to about 1.0%.

In lotion or cream formulations, zinc pyrithione (Zinc Omadine) is compatible with free fatty acids as the zinc molecule is chelated by the pyrithione and unavailable to couple with the free fatty acids. Zinc Omadine may be added to the formula in the presence of long-chain alcohols, long-chain unsaturated fatty acids, medium-chain saturated fatty acids, and/or their esters with an emulsifier. Zinc Omadine can be incorporated at a concentration of about 0.0001% to about 5.0% (w/v), more preferably in a range of from about 0.5% to about 4% (w/v), and most preferably from about 1.0% to about 2.0% (w/v).

It has been surprisingly found that bispyrithione (Omadine Disulfide) is highly soluble in the solutions suggested for the quick-kill component, especially alcohol. For example, when bispyrithione is added in about 2.5% to 3% (w/v) to a solution of Emery 644 fatty acids in a 70% (v/v) n-propanol solution, bispyrithione fully dissolves and substantially maintains full activity of both the fatty acids and bispyrithione. That bispyrithione would dissolve in the n-propanol and fatty acid solutions is unexpected. Bispyrithione, when added as the persistent component of the present invention, is preferably added in a range of about 0.0001% to about 5.0% (w/v), more preferably from about 0.5% to about 4% (w/v), and most preferably from about 1.5% to about 2.5% (w/v). Bispyrithione is effective against all microorganisms.

The second group of nitrogen compounds are alkyl or aryalkyl amines (Group II). This group exhibits significant substantivity and antimicrobial effects.

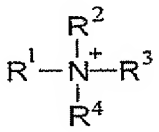
The third group of nitrogen compounds are quaternary ammonium compounds (Group III). These compounds are effective detergents which have the ability to form a film, exhibit wide microbicidal activity, and depending on the location of the nitrogen group, exhibit profound persistence. One type of quaternary ammonium compounds of interest include straight chain ammonium salts. Preferably, ammonium salts useful in the practice of the present invention may be characterized as water-soluble tertiary ammonium salts of the group consisting of:



wherein it is preferred that the R^1 straight alkyl group have a chain length of eight to fourteen. The X^- salt is preferably acetate or chloride. Examples would include octylammonium acetate, decylammonium chloride, and tetradecylammonium chloride. Particularly preferred is dodecylammonium chloride. A preferred dodecylammonium chloride concentration is from about 0.0001% to about 25.0% (w/v), more preferred from about 0.01% to about 15.0% (w/v), and most preferred from about 0.5% to about 10.0% (w/v). A 40% concentration of a dodecylammonium hydro-alcoholic solution has a pH of 1.88 and can be used to lower the pH of the

antiseptic composition. The nitrogen may have chemical groups of different chain length attached to it wherein R^1, R^2 and R^3 are saturated or unsaturated aliphatic radicals optionally containing ether or amide linkages and/or pendant hydroxyl groups and the total number of carbon atoms in $R^1 + R^2 + R^3$ does not exceed 28; and wherein X is either acetate or chloride. R^2 and R^3 can be methyl groups.

Another type of quaternary ammonium compound of the present invention may be of the group consisting of:



where R^1, R^2, R^3, and R^4 are alkyl groups that may be alike or different, substituted or unsubstituted, saturated or unsaturated, branched or unbranched, and cyclic or acyclic, and that may contain ether, ester or amide linkages; they may be aromatic or substituted aromatic groups. The nitrogen atom plus the attached alkyl groups forms the positively-charged portion, which is the functional part of the molecule. The portion attached to the nitrogen by an electrovalent bond may be any anion, but is usually chloride or bromide to form the salt. This group of compounds would provide quick-kill, detergency, and persistence (depending on the location of the nitrogen). Examples of quaternary ammonium compounds preferred for the antiseptic are dodecyldimethyl-ammonium chloride,

cetyldimethylammonium chloride, cetylpyridium chloride, benzalkonium chloride, benzethonium chloride, substituted benzalkonium chloride, twin chain quats, domiphenbromide, and N-(3-chloroallyl) hexaminium chloride. The polymeric polyquaternary ammonium compounds and free radical polymeric quaternary ammonium compounds can be used if the attached groups have microbicidal activity. The aromatic quaternary ammonium compounds preferred for the present invention are cetylpyridium chloride or Hyamine 1622. These may be used in concentrations of about 0.01% to about 5.0% (w/v), more preferably about 0.05% to about 3.0% (w/v), and most preferably about 0.1% to about 2.0% (w/v).

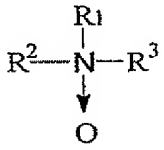
The fourth group of nitrogen compounds consists of biguanides and bisbiguanides (Group IV). This group exhibits quick-kill and the best substantivity heretofore developed. The prototype compound for this group is chlorhexidine gluconate. The nitrogen groups are between the aromatic rings, however, and substantivity is not as great as would be expected in a compound such as octenidine hydrochloride where nitrogen is more exposed with less steric hindrance.

The fifth group of nitrogen compounds are amine oxides (Group V). Amine oxides are utilized for quick-kill, detergency, non-irritating, penetrating and persistence. Amine oxides have been used before in compositions which contact the skin, most notably as solubilizers or emulsifying agents in certain cosmetic formulations and shampoos. The compounds are described as having many desirable attributes of particular value in emulsification, cleansing, and detergency. They are

further described as having a non-irritating and even anti-irritating effect on the skin. The water soluble amine oxides can be used to enhance penetration of therapeutic agents into and/or through the skin.

The amine oxides are potent antimicrobial agents, depending mainly on the chain length of the hydrophobic alkyl and is only moderately influenced by other substituents of the polarized N-O group. Significantly lower activity is found for amine oxides containing an alkyl group shorter than C12, and maximum activity is found for 4-hexadecyl compounds. Pertinent to all the amine oxides is the position of the nitrogen atom and in its ability to bind and produce profound substantivity.

In general, there are two broad categories of amine oxides, straight alkyl chain and aromatic. Both groups are pertinent to this antiseptic invention. The straight chain amine oxides would be exemplified by:



where R^1 is an alkyl radical of from about 6 to about 18, preferably from about 8 to about 14 carbon atoms. R^2 and R^3 are preferably methyl groups, however one or both R groups can be an alkyl radical of from about 8 to about 18 carbon atoms, preferably from about 10 to about 14 carbon atoms or one R group can be methyl.

The nitrogen - oxygen bond is represented by an arrow representing a semi-polar bond. Specific examples of amine oxide detergents include dodecyldimethylamine oxide, tridecyldimethylamine oxide, tetradecyl-dimethylamine oxide, pentadecyldimethylamine oxide, dececyldimethylamine oxide, heptadecyldimethylamine oxide, octadecyldimethylamine oxide, dodecyl-diethylamine oxide, octadecyldibutylamine oxide, dodecyldibutylamine oxide, tetradecyldibutylamine oxide, octadecyldibutylamine oxide, bis(2-hydroxy-ethyl)dodecylamine oxide, dimethyl-(2-hydroxydodecyl) amine oxide, 3,6,9-trioxoctandecyl dimethyl amine oxide, and 3-dodecoxy-2-hydroxy propyl-di(2)-hydroxyethyl) amine oxide. Salts of straight chain alkyl amine oxides can also be used.

There are four groups of aromatic amine oxides that could be used in the antiseptic invention for quick-kill and substantivity. These include pyrrolidine-N-oxides, piperidine-N-oxides, perhydroasepine-N-oxides, and morpholine-N-oxides.

In each of the aromatic amine oxides the antibacterial effectiveness is determined by the length of the alkyl group attached to the nitrogen. Morpholine-N-oxides are useful penetration enhancing agents, for example, Azone. Alkyl groups of between eight and twenty carbon atoms may be useful; however, it is preferable to use chain lengths of twelve to eighteen.

Preferred amine oxides include the linear alkylamine oxides, pyrrolidine-N-oxides, piperidine-N-oxides, perhydroasepine-N-oxides and morpholine N-

oxides or their salts. Preferred concentrations for these nitrogen compounds in the present invention are from about 0.001% to about 5.0% (w/v), more preferably from about 0.01% to about 5.0% (w/v), and most preferably from about 0.05% to about 3.0% (w/v). Another group of nitrogen compounds which could be used in the antiseptic formulation are quinolines (Group VI). Quinolines useful for the present invention have nitrogen which is not inhibited by steric hindrance and able to bind to produce substantivity formulation.

Another group of nitrogen compounds which could be used in the present invention are antibiotics (Group VII). Antibiotics such as neomycin which have amino groups available to bind to structures in or on the surface of the skin to produce substantivity could be used in the antiseptic formulation. When neomycin is combined with alcohols and lipids, it is foreseen that this combination would be especially effective as a substitute for bispyrithione in neonates through adolescents.

A final group of nitrogen compounds consists of combinations of the nitrogen compounds listed above (Group VIII). In the antiseptic formulation it is desirable to have both quick-kill and persistence. Some of the nitrogen compounds lack quick-kill but have outstanding persistence, e.g., pyridine-N-oxides (Omadines). Some of the nitrogen compounds have outstanding quick-kill and persistence, e.g., dodecylammonium chloride and Hyamine 1622. Thus, any combination of ingredients from Groups I through VII could be used in the antiseptic formulation to achieve

the desired effect of quick-kill and persistence. When the nitrogen atom is bound to the site of application, it is foreseen that the alkyl group will be projected above the site. Thus, the alkyl group would help produce a hydrophobic, lipophilic surface analogous to the function of the pure lipids.

Other ingredients may be added to improve specific types of antiseptic formulations. For example, it is foreseen that glycyrrhetinic acid would be preferably added to skin formulations to act as an anti-inflammatory agent. The addition of hyaluronic acid to the antiseptic would be beneficial in wound and burn antiseptics. For treatment of viruses, 2-deoxy-D-glucose may be added to increase the antiviral activity of the antiseptic.

The antiseptic may also utilize various penetration controlling agents to control the degree to which the antiseptic composition penetrates through the stratum corneum, epidermis and dermal layers. For the antiseptic to permeate throughout the epidermis, the preferred compositions of the present invention may utilize a membrane penetration component(s). These components helps to ensure that the microorganisms that are hidden in the pilosebaceous glands, sweat ducts and in the superficial and deep layers of the stratum corneum are also killed with the surface treatment. Consequently, preferred membrane penetration compounds are also microbicidal. Some of the preferred penetrating compounds are unsaturated long-chain fatty acids, esters of fatty acids, propylene glycol, medium-chain saturated fatty acids and medium-chain alcohols

(C8 through C14). When it is important to inhibit penetration beyond the basal cell layer this is easily accomplished by incorporating combinations of mineral oil, petrolatum, or cetyl and stearyl alcohols. When it is important to prohibit irritants from contacting the skin, this may be accomplished by incorporating polymers of linoleic acid.

Improved kill of microorganisms is also found if a chelating agent component is incorporated. Preferably the chelating agent is a calcium and magnesium chelating agent that also tends to lower the pH of the composition. Suitable chelating agents of this type include polyphosphoric acid, citric acid, phosphonic acids and phosphoric acids. Useful chelating agents include: aminopolycarboxylic acids (such as hydroxyethyl imino diacetic acid, nitrilo triacetic acid, ethylene diamine tetraacetic acid, hydroxyethyl ethylenediamine triacetic acid, and diethylene triamine pentacetic acid); alpha-hydroxy acids (such as tartaric acid, citric acid, and gluconic acid); and condensed phosphates and phosphonates. The preferred chelating agents for use in the present invention are dependent on the final use. At an acid pH, phosphoric or phosphonic acids are preferable. At neutral pH, either a mixture of phosphonic acids and their salts, or ethylenediamine tetraacetic acid and pharmaceutically acceptable salts thereof, especially sodium ethylene diamine tetraacetate are preferable. Other useful calcium chelating components include ethane-1-hydroxy-1,1'-diphosphonic acid, methane diphosphonic acid, hydroxy methane diphosphonic acid and mixtures thereof.

It is also preferred to incorporate an antioxidant component into the compositions of the present invention to prevent saturation of the unsaturated fatty acids. Suitable antioxidants include betahydroxy toluene, Vitamin E, Vitamin C, alpha-tocopherol, and propyl gallate or mixtures containing propyl gallate such as Tenox PG or Tenox S1 (Eastman Chemical Co., Kingsport, TN). A preferred antioxidant is propyl gallate which may be increased above antioxidant levels to achieve a potent anti-inflammatory effect. The gallic acid esters, especially methyl gallate, also may be used to exert an anti-viral effect, especially on the herpes virus and cytomegalovirus. The gallic acid esters may also function to prevent damage to the skin from ultraviolet light or radiation damage.

Antiseptic products that are intended for chronic use can be detrimental to the skin, particularly agents that are frequently applied to the hands, e.g., health care personnel hand washing agents. Cetyl and stearyl alcohols are common components of lotions and creams. When cetyl and stearyl alcohols are added to the n-propanol antiseptic formula they precipitate at relatively cool ambient temperatures, making them unsuitable. However, if cetyl and stearyl alcohols are added when ethoxylated, then a stable solution can be obtained. Particularly preferred products are the emulsifying waxes Polawax or Polawax 31 (Croda, Inc., Parsippany, NJ), or ethoxylated fatty alcohols such as Eumulgin B2 (Henkle Corporation, Emery Group, Cincinnati, OH). When Polawax is added up to a concentration of four percent in alcohol the antiseptic

formulation remains clear. When Polawax is added in increasing amounts with lipids, the antiseptic becomes an emulsion.

Particularly preferred are Polawax concentrations of six to twelve percent. When excess Polawax is added, it causes the antiseptic to become very viscous or even a solid. When appropriate amounts of Polawax are used, the emulsion provides a mechanism of using previously insoluble ingredients, e.g., Zinc Omadine which may be suspended into a stable emulsion. The cosmetic appeal and activity may be significantly enhanced by using long-chain alcohols or esters in an emulsion formulation. Polymers of long-chain unsaturated fatty acids may be used to produce anti-irritation effects.

A coloring and texture component may also be utilized within the composition for different embodiments. In particular, a thickener may be utilized for certain embodiments to decrease the quick evaporation of alcohols especially when used as the quick-kill component, and to keep various low viscosity fluids from quickly running off of the surface being treated. An effective thickener has been found to be hydroxypropyl cellulose sold under the trademark Klucel by Aqualon, Wilmington, DE. When the compositions are utilized for surgery, dyes may be incorporated such that the area treated by the antiseptic may be quickly visualized by the medical practitioners to ensure application. In some of the embodiments a formulation may be varied so as to effectively modify the composition into a cream for certain purposes. The

components of the present invention may be made mucoadhesive with sodium carboxymethyl cellulose, polyethylene oxides such as Polyox WSR 301, propylene glycol, and polyethylene glycol 8,000 to make a gel. This would facilitate treatment for lesions in the mouth, such as aphthous ulcers. Also, this combination would be an effective antiseptic to apply to the periurethral area to prevent nosocomial infections associated with a chronic indwelling Foley catheter. Certain vaginal applications would be enhanced with the addition of mucoadhesive components.

The antiseptic compositions of the present invention may also be combined with conventional over-the-counter (OTC) or prescription ingredients to achieve salutary effects. Current OTC treatment for acne would include salicylic acid, sulfur, resorcinol, resorcinol monoacetate, and benzoyl peroxide, while agents restricted to prescription, e.g., antibiotics include trinetoin, erythromycin, tetracycline, clindamycin or their combinations. Current treatment for topical fungal infections including undecylenate, miconazole, clotrimazole, tolnaftate, terconazole, and butoconazole may be combined with ingredients of the present invention. Current OTC treatment for the prevention of sunburn include para-aminobenzoic acid, ethylhexyl p-methoxycinnamate, and cinnamate. The ingredients of the present invention may be combined with agents for minor wound care including OTC agents such as neomycin, bacitracin, polymyxin B, and Neosporin, or antibiotics. Other combinations would include product enhancing agents for a soothing,

cooling, detergent, astringent, antipruritic effect or anti-inflammatory agents (OTC or prescription strength corticosteroids). The ingredients of this invention may be combined with anti-metabolites, cytostatic agents, keratolytic agents, or tar products. The compounds of this invention may be combined with OTC or prescription eye and ear ingredients.

While low pH is a distinct advantage in quick kill, it is foreseen that too low a pH could be detrimental in specific formulations of the antiseptic compositions of the present invention. For example, too low a pH could cause hydrolysis of the thickener (Klucel), ester formation of the fatty acids, and the glycerol monolaurate (Lauricidin).

Antiseptic compositions of the present invention have been are formulated to provide the following advantages: are antimicrobial, both immediately and long-term; provide a very high ratio of kill, preferably a kill to zero; provide a broad spectrum of antimicrobial kill; are not irritating to skin of humans and mammals and can be readily adapted for usage on other tissues; are adapted to penetrate and bind into the epidermis and kill microorganisms therein; are adapted to bind to the skin surface and kill microorganisms therein; have substantial persistence both in terms of maintaining a low quantity of microorganisms on tissue treated by the compositions for a substantial period of time and not allowing the level of microorganisms on or in the tissue to return to normal for a substantial period of time; are user-friendly, having odor, tactile qualities and other

characteristics which are pleasant to those both applying and receiving the compositions; are adaptable or modifiable to a wide range of medical uses as antiseptics including use on sensitive tissues; and are relatively easy to prepare, stable in shipment and especially effective for their intended purposes.

Other objects and advantages of this invention will become apparent from the following descriptions wherein are set forth, by way of illustration and example, certain embodiments of this invention. It is to be understood that while certain forms of the present invention have been illustrated and described herein, it is not to be limited to the specific forms or arrangement of parts described and shown.

EXAMPLE 1: PREPARATION OF A MINIMUM REQUIREMENT ANTISEPTIC WITHOUT FATTY ACIDS

To prepare the antiseptic as indicated in Table I, initially mix approximately 95% of the volume of n-propanol with the thickening agent Klucel. To hydrate the Klucel, stir for 2-3 hours with equipment that produces high shear, or overnight with equipment that only produces low shear. Add the additional 5% of n-propanol, and while continuously stirring, add the appropriate amount of the emulsifier. Adjust the pH as required, add the appropriate amount of Zinc Omadine, and q.s. to 100% with deionized water.

Table I. EXEMPLARY FORMULATION FOR MINIMUM REQUIREMENT ANTISEPTIC

COMPONENT	CONCENTRATION (%)
ALCOHOL	
N-Propanol[a]	70
EMULSIFIER	
Polawax[b]	6
PRESERVATIVE	
Zinc Omadine[b,c]	2
THICKENING AGENT	
Klucel[b]	1
pH ADJUSTING AGENT	
Phosphoric acid[b]	2

[a] Concentration in percent (v/v).

[b] Concentration in percent (w/v).

[c] Quick-kill and persistent agent.

EXAMPLE 2: PREPARATION OF MINIMUM REQUIREMENT ANTISEPTIC WITH FATTY ACIDS

To formulate an antiseptic containing fatty acids, the ingredients given in Table II, initially mix approximately 95% of the volume of n-propanol with the thickening agent Klucel. To hydrate the Klucel, stir for 2-3 hours with equipment that produces high shear, or overnight with equipment that only produces low shear. Add the additional 5% of n-propanol, and while continuously stirring, add the appropriate amount of the emulsifier, fatty acid, and antioxidant. Adjust the pH as required, add the appropriate amount of Zinc Omadine, and q.s. to 100% with deionized water.

Table II. EXEMPLARY FORMULATION FOR MINIMUM REQUIREMENT ANTISEPTIC

COMPONENT	CONCENTRATION (%)
ALCOHOL	
N-Propanol[a]	70
EMULSIFIER	
Polawax[b]	6
FATTY ACID	
Emery 305[b]	5
PRESERVATIVE	
Zinc Omadine[b,c]	2
THICKENING AGENT	
Klucel[b]	1
pH ADJUSTING AGENT	
Phosphoric acid[b]	2
ANTIOXIDANT	
Propyl gallate[b]	0.1

[a] Concentration in percent (v/v).

[b] Concentration in percent (w/v).

[c] Quick-kill and persistent agent.

EXAMPLE 3: IN VITRO MEASUREMENT OF ANTIMICROBIAL ACTIVITY OF OMADINE AND OTHER POTENTIAL COMPONENTS OF NEW ANTISEPTIC FORMULATIONS

Seven compounds or mixtures were tested including bispyrithione (Zinc Omadine), two free fatty acid hydrolysates (Emery 315 and Emery 644), acetic acid, propylene glycol, and two antiseptic formulations that contained 2.5% bispyrithione and 3.0 % fatty acids,

with or without 0.25% Klucel (AS+K and AS-K, respectively). The pH of the antiseptic mixtures was 2.7-2.8.

Over 200 bacterial and fungal isolates from clinical patient infections at the University of Iowa Hospitals and Clinics (Iowa City, Iowa) were used to determine antimicrobial activity. Each strain was identified by routine methods (Vitek Systems, API, etc.) in use in the Medical Microbiology Division laboratories. The following species were processed: *Staphylococcus aureus* (10 strains, five resistant to methicillin), coagulase-negative staphylococci (10 strains representing four species, five resistant to methicillin), *Enterococcus* spp. (10 strains), *Streptococcus pyogenes* (10 strains), beta-hemolytic streptococci groups B, C, and G (10 strains), *Corynebacterium jeikeium* (10 strains), *Corynebacterium parvum* (previously *Propionibacterium acnes*) (10 strains), *Escherichia coli* (10 strains representing two species), *Enterobacter* spp. (10 strains), *Klebsiella* spp. (10 strains, representing two species), *Pseudomonas aeruginosa* (10 strains), *Citrobacter* spp. (10 strains), indole-positive *Proteeae* (10 strains), *Salmonella/Shigella* spp. (10 strains), *Serratia marcescens* (10 strains), *Acinetobacter* spp. (10 strains), *Xanthomonas maltophilia* (10 strains), *Prevotella bivia-disiens* (10 strains), *Bacteroides fragilis* (10 strains), *Gardnerella vaginalis* (10 strains), *Lactobacillus* spp. (10 strains), *Mobiluncus* spp. (10 strains), *Aspergillus* spp. (5 strains),

Candida albicans (5 strains), *Candida* spp. (5 strains), and dermatophytes (5 strains).

All susceptibility testing was performed by methods conforming to the recommendations of the National Committee for Clinical Laboratory Standards (NCCLS). Mueller-Hinton agar (Difco Laboratories, Detroit, MI) was used with supplemental 5% sheep erythrocytes for fastidious species (streptococci, corynebacteria). Dilution schedules were selected based on preliminary pilot studies covering a dilution range of 10% to 0.001% solutions of each compound or mixture. The following dilution ranges were used for each substance/mixture following pilot study experiments: 1) bispyrithione, 0.25% to 0.001%, or 250 to 1 microgram/ml; 2) acetic acid and the two antiseptic mixtures, 4% to 0.015%; and 3) propylene glycol and two fatty acid hydrolysates, Emery 644 and Emersol 305, 16% to 0.25%. Note that the antiseptic solutions and fatty acids were listed as % solutions but actually represent dilutions of the provided formulation(s), e. g. 1:25 to 1:6400.

The pH of the agar medium was 7.2 to 7.4 conforming to the NCCLS recommendations. Therefore, the antimicrobial action of several of these substances which perform maximally at acidic pH ranges was potentially underestimated because of testing at standard microbiology pH levels favoring the growth of pathogenic organisms.

Table III lists the minimum inhibitory concentrations (MICs) obtained in the pilot study in which 10% to 0.001% solutions were tested against

laboratory strains of seven bacteria and one yeast. From these results, the assay dilution ranges were selected.

When the antiseptic formulations (2.5% Zinc Omadine and 3.0% fatty acids in n-propyl alcohol) with and without a thickening agent (0.25% Klucel) were tested as a dilution of the final concentration, excellent inhibition was observed as shown in Table III. All gram positive organisms were inhibited at less than 0.1% dilution, and all gram negative organisms, at less than 1.0% dilution.

Table III. DILUTION MIC TEST RANGING PILOT STUDY FOR SEVEN ANTIMICROBIAL AGENTS OR MIXTURES AGAINST BACTERIA AND YEAST CONTROL STRAINS

	MIC in % dilution for various antimicrobial and mixtures[a]						
Organism	Omadine	Emery 644	Emersol 315	Antiseptic - Klucel	Antiseptic + Klucel	Acetic Acid	Propylene Glycol
S. aureus 25923	0.001	1	1	0.1	0.1	1	>10
S. aureus 29213	0.001	1	1	0.1	0.1	1	>10
S. epidermidis 7872	0.001	1	1	0.1	0.1	1	>10
E. faecalis 29212	0.001	1	10	0.1	0.1	1	10
E. coli 25922	0.01	10	>10	0.1	0.1	1	10
P. aeruginosa 27853	0.1	10	>10	1	1	1	10
C. albicans 8501	0.01	10	>10	0.01	0.01	1	10

[a] Dilution schedule in Log10 intervals of the provided solution (1:100 dilution of acetic acid = 0.36% (w/v) and a 1% solution Zinc Omadine = 1000 μg/ml.

Table IV. ANTIMICROBIAL ACTIVITY OF SEVEN AGENTS OR MIXTURES TESTED AGAINST 109 CLINICAL BACTERIAL ISOLATES

Organism (No. tested)	Antimicrobial Agent	MIC as a % solution[a] MIC50	MIC90	Range
GRAM POSITIVE BACTERIA				
S. aureus (10)	Bispyrithione	<0.001	<0.001	<0.001
	Emery 644	<0.25	<0.25	<0.25
	Emersol 315	<0.5	0.5	<0.25-0.5
	AS-K	<0.015	<0.015	<0.015
	AS+K	<0.015	<0.015	<0.015
	Acetic acid	0.12	0.12	<0.06-0.12
	Propylene glycol	16	16	8-16
Coagulase-negative staphylococcus (10)[b]	Bispyrithione	<0.001	<0.001	<0.001-0.002
	Emery 644	<0.25	0.5	<0.25-0.5
	Emersol 315	0.5	1	<0.25-1
	AS-K	<0.015	0.03	<0.015-0.03
	AS+K	<0.015	0.03	<0.015-0.06
	Acetic acid	0.12	0.12	<0.06-0.12
	Propylene glycol	8	8	4-8
Enterococcus spp. (10)[c]	Bispyrithione	0.002	0.002	<0.001-0.002
	Emery 644	0.5	0.5	<0.25-0.5
	Emersol 315	0.5	0.5	<0.25-0.5
	AS-K	0.06	0.06	0.03-0.06
	AS+K	0.06	0.06	0.03-0.06
	Acetic acid	0.12	0.12	0.12
	Propylene glycol	8	8	8

Organism (No. tested)	Antimicrobial Agent	MIC as a % solution[a] MIC50	MIC90	Range
S. pyogenes (9)	Bispyrithione	0.002	0.002	<0.001-0.002
	Emery 644	1	1	0.5-1
	Emersol 315	1	1	1
	AS-K	0.06	0.12	0.03-0.12
	AS+K	0.06	0.12	0.03-0.12
	Acetic acid	<0.06	<0.06	<0.06
	Propylene glycol	16	16	16
β-haemolytic streptococci GR. B, C and G (10)[d]	Bispyrithione	<0.001	<0.001	<0.001
	Emery 644	1	1	0.5-1
	Emersol 315	1	1	1
	AS-K	0.03	0.03	0.03
	AS+K	0.03	0.03	<0.015-0.03
	Acetic acid	0.12	0.12	0.12
	Propylene glycol	16	16	16
C. jeikeium (10)	Bispyrithione	0.002	0.002	0.002-0.004
	Emery 644	1	1	0.5-1
	Emersol 315	1	1	1
	AS-K	0.12	0.12	0.12
	AS+K	0.06	0.06	0.06-0.12
	Acetic acid	0.12	0.12	<0.06-0.12
	Propylene glycol	8	16	4-16

Organism (No. tested)	Antimicrobial Agent	MIC as a % solution[a] MIC50	MIC90	Range
C. parvum (10)	Bispyrithione	0.008	0.008	0.004-0.008
	Emery 644	1	1	1
	Emersol 315	2	2	2
	AS-K	0.12	0.12	0.12-0.25
	AS+K	0.12	0.25	0.12-.025
	Acetic acid	0.12	0.12	0.12
	Propylene glycol	16	16	16
GRAM-NEGATIVE BACTERIA				
E. coli (10)	Bispyrithione	<0.001	<0.001	<0.001
	Emery 644	1	2	1-2
	Emersol 315	16	16	8-16
	AS-K	0.03	0.03	0.03
	AS+K	0.03	0.03	0.03
	Acetic acid	<0.06	<0.06	<0.06
	Propylene glycol	16	16	16
Enterobacter spp. (10)[e]	Bispyrithione	0.002	0.002	0.002
	Emery 644	2	4	2-4
	Emersol 315	>16	>16	>16
	AS-K	0.06	0.06	0.06
	AS+K	0.06	0.06	0.06-0.12
	Acetic acid	<0.06	<0.06	<0.06
	Propylene glycol	16	16	16

Organism (No. tested)	Antimicrobial Agent	MIC as a % solution[a] MIC50	MIC90	Range
Klebsiella spp. (10)[f]	Bispyrithione	0.002	0.002	<0.001-0.002
	Emery 644	2	4	2-4
	Emersol 315	>16	>16	16->16
	AS-K	0.06	0.06	0.03-0.12
	AS+K	0.06	0.06	0.03-0.12
	Acetic acid	<0.06	<0.06	<0.06
	Propylene glycol	16	16	16
P. aeruginosa (10)	Bispyrithione	0.12	0.12	0.12
	Emery 644	2	4	2-4
	Emersol 315	16	16	8-16
	AS-K	1	1	1
	AS+K	0.5	1	0.5-1
	Acetic acid	<0.06	<0.06	<0.06
	Propylene glycol	8	16	8-16

[a] Bispyrithione 0.001% solution. Other MICs represent (w/v) calculated % solutions.

[b] Also *S. simulans* (2 strains).

[c] Includes *E. faecalis* (5 strains), *E. faecium* (2 strains), *E. avium* (1 strain), and *E. raffinosus* (1 strain).

[d] Includes serogroups B (3 strains), C (1 strain) and G (6 strains).

[e] Includes *E. cloacae* (7 strains) and *E. aerogenes* (3 strains).

[f] Includes *K. oxytoca* (2 strains) and *K. pneumoniae* (8 strains).

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Table V. ANTIMICROBIAL ACTIVITY OF THREE AGENTS TESTED AGAINST SEVERAL ADDITIONAL BACTERIAL ISOLATES

Organism (no tested)	Antimicrobial Agent	MIC as a % solution[a] MIC50	MIC90	Range
GRAM NEGATIVE BACTERIA				
Citrobacter ssp. (10)[b]	Bispyrithione	0.002	0.002	0.002-0.004
	Emery 644	2	2	2
	AS+K	0.06	0.06	0.03-0.12
Indole-positive *Proteeae* (10)[c]	Bispyrithione	0.004	0.015	0.004-0.015
	Emery 644	2	2	2
	AS+K	0.12	0.5	0.12-0.5
Salmonella/Shigella (10)[d]	Bispyrithione	0.002	0.002	0.002
	Emery 644	4	4	2-4
	AS+K	0.06	0.06	0.06
S. marcescens (10)	Bispyrithione	0.004	0.004	0.002-0.004
	Emery 644	4	4	4
	AS+K	0.12	0.12	0.06-0.12
Acinetobacter ssp. (10)[e]	Bispyrithione	0.004	0.015	<0.001-0.015
	Emery 644	1	2	1-2
	AS+K	0.25	0.5	0.03-1
X. maltophilia (10)	Bispyrithione	0.015	0.03	0.004-0.03
	Emery 644	2	4	2-4
	AS+K	0.5	1	0.12-1

Organism (no tested)	Antimicrobial Agent	MIC as a % solution[a] MIC50	MIC90	Range
VAGINOSIS-ASSOCIATED BACTERIA				
P. bivia-disiens (10)	Bispyrithione	<0.001	<0.001	<0.001
	Emery 644	0.5	0.5	<0.25-1
	AS+K	<0.015	0.03	<0.015-0.03
B. fragilis (10)	Bispyrithione	0.002	0.002	<0.001-0.002
	Emery 644	1	1	0.5-1
	AS+K	0.06	0.06	0.03-0.06
G. vaginalis (10)	Bispyrithione	<0.001	0.002	<0.001-0.002
	Emery 644	<0.25	<0.125	<0.25
	AS+K	0.06	0.06	<0.015-0.12
Lactobacillus spp. (10)	Bispyrithione	<0.001	<0.001	<0.001-0.004
	Emery 644	2	2	<0.25-2
	AS+K	<0.015	<0.015	<0.015-0.25
Mobiluncus spp. (10)	Bispyrithione	0.002	0.002	<0.001-0.002
	Emery 644	<0.25	<0.25	<0.25
	AS+K	0.12	0.12	<0.015-0.12
YEAST AND FUNGI				
Aspergillus spp. (5)[f]	Bispyrithione	<0.001		<0.001-0.015
	Emery 644	>16		4->16
	AS+K	1		<0.015-1
C. albicans (5)	Bispyrithione	<0.001		<0.001
	Emery 644	>16		>16
	AS+K	<0.015		<0.015

Organism (no tested)	Antimicrobial Agent	MIC as a % solution[a] MIC50	MIC90	Range
Candida spp. (5)[g]	Bispyrithione	<0.001		<0.001
	Emery 644	2		0.05->16
	AS+K	<0.015		<0.015
Dermatophytes (5)[h]	Bispyrithione	<0.001		<0.001
	Emery 644	0.5		0.5
	AS+K	<0.015		<0.015

[a] Bispyrithione 0.001% solution. Other MICs represent (w/v) calculated % solutions.

[b] Includes *C. diversus* (6 strains) and *C. freundii* (4 strains).

[c] Includes *M. morganii* (5 strains) and *Providencia* spp. (5 strains, 2 species).

[d] Includes *S. enteritidis* (6 strains) and *S. sonnei* (4 strains).

[e] Includes *A. anitratus* (8 strains) and *A. lwoffii* (2 strains).

[f] Includes *A. flavus* (2 strains), *A fumigatus* (2 strains), and *A. terreus* (1 strain).

[g] Includes *C. glabrata* (1 strain), *C. krusei* (1 strain), *C. lusitaniae* (1 strain), *C. parapsilosis* (1 strain), and *C. tropicalis* (1 strain).

[h] Includes one strain each of *M. canis*, *M. gypseum*, *T. mentagrophytes*, *T. rubrum*, and *Trichophyton* spp.

Table VI. EFFECTS OF 5% SHEEP BLOOD ON THE AGAR DILUTION MICs OF THE ANTISEPTIC SOLUTION PLUS KLUCEL

Organism	MIC as a % Antiseptic Solution:	
	Agar + 5% Sheep[a]	Agar Alone
C. albicans (8501)	0.008	0.015
E. coli (25922)	0.015	0.015
E. faecalis (00049)	0.015	0.015
P. aeruginosa (27853)	0.25	0.25
S. aureus (29213)	0.03	0.03
S. aureus (25923)	0.03	0.03

[a] Agar supplemented with 5% sheep blood.

Results for seven antimicrobial agents against a wide variety of the clinical bacterial isolates were tabulated as the concentration inhibiting 50% and 90% of the tested organisms and are presented in Table IV. The range of MICs is also listed for each tested substance.

Antimicrobial activities of bispyrithione, fatty acids, and antiseptic plus Klucel were measured using clinical isolates of several microorganisms, including additional gram positive bacteria, vaginosis-associated bacteria, yeasts and molds. Table V presents the results as the concentration inhibiting 50% and 90% of the tested organisms, with the MIC range also provided.

These in vitro susceptibility tests using NCCLS procedures confirm the spectrum and level of potency previously stated by the bispyrithione manufacturer (Olin Chemicals). Bispyrithione has a spectrum of activity inhibiting all significant gram positive pathogens at <0.004%, or <40 micrograms/ml. Similarly, with the exception of *Pseudomonas* and *Xanthomonas* spp., all enteric bacilli tested had MIC's at <0.004%, or <40 micrograms/ml. *Pseudomonas aeruginosa* and *Xanthomonas maltophilia* had higher MICs at <0.12% (120 micrograms/ml) and 0.15% (150 micrograms/ml), respectively. *Aspergillus* spp., *Candida albicans*, other *Candida* spp., and the dermatophytes were inhibited at a bispyrithione concentration of <0.001%, or 10 micrograms/ml.

The fatty acid hydrolysates had a comparable spectrum of activity to that of bispyrithione. The Emery 644 was generally equal to or 2-fold superior in potency to Emersol 315 when tested against gram positive organisms. All gram positive bacteria tested were inhibited by the 1:50 dilution of the original hydrolysate. Emery 644 was also more active than Emersol 315 versus gram negative bacilli (4- to >8-fold) and *Candida albicans*. All Emery 644 MIC's were <4%, or a 1:25 dilution of the provided full-strength hydrolysate.

When the antiseptic formulations of 2.5% bispyrithione and 3.0% fatty acids in propyl alcohol with and without Klucel were tested as a dilution of the final concentration, excellent inhibition was

observed. All gram positive and gram negative organisms were inhibited at <0.12% (1:800 dilution) and <1% (<1:100 dilution), respectively. Vaginosis-associated organisms were effective at <0.025% (<1:400 dilution), and fungi at <1% (<1:100 dilution).

To assess the effect of blood on the antimicrobial activity of the antiseptic solution consisting of 2.5% bispyrithione and 3.0% fatty acids in n-propyl alcohol plus Klucel, the NCCLS procedure was performed using Mueller Hinton agar plates with and without 5% sheep blood. Antimicrobial activity was measured as the concentration inhibiting 50% of the tested organisms. As shown in Table VI, comparisons of MICs for the antiseptic with Klucel determined on media with and without 5% sheep erythrocytes failed to demonstrate any significant differences. Small amounts of blood appear to not affect the potency of fatty acids or the bispyrithione.

EXAMPLE 4: PREPARATION OF HEALTH CARE PERSONNEL HAND WASH AND EXEMPLARY MEASUREMENT OF ANTIMICROBIAL ACTIVITY THEREOF

Five formulations of health care personnel hand wash antiseptic were prepared according to the procedure given in Example 2 by combining the ingredients given below in Table VII, adjusting the pH to 3.00-3.50 with either phosphoric acid, Dequest 2010 or citric acid, and q.s. to 100% with deionized water. The final concentrations are indicated either as percent (v/v) or percent (w/v).

A test was performed utilizing Formulation #5 outlined in Table VII, according to the Food and Drug Administration guidelines for approval of a health-care personnel handwash agent. *Federal Register* 59:31448-31450(June 17, 1994). The test consists of ten cycles of contamination with a contaminating suspension of *Serratia marcescens* ATCC 14756 (American Type Culture Collection, Rockville, MD) at 6 x 10^8 colony-forming units per milliliter (cfu/ml) followed by a wash with the test product and subsequent culturing after the first contamination, first wash, fifth wash and tenth wash. The object of the test is to reduce the number of contaminating transient microorganisms on the hands of health care personnel as much as possible without producing a deleterious effect on the hands of the user.

In the antiseptic wash procedure, three milliliters of the novel antiseptic was placed in the palm of one hand, and the antiseptic was then rubbed onto all surfaces of the hands, including the interdigital spaces. Since the antiseptic formulations tested air-dry in approximately 45 seconds, no rinsing with water was required or desirable. After the hands were held in the air for approximately ten minutes, separate cultures were obtained from the right and left hands according to a modified "glove juice method." Loose fitting gloves were placed over the right and left hand, and 50 to 100 ml of sterile sampling solution (0.4 g potassium phosphate, monobasic, 10.1 g sodium phosphate, dibasic, and 1 g Triton X-100 per

Table VII. EXEMPLARY FORMULATIONS OF HEALTH-CARE PERSONNEL HAND WASH

	CONCENTRATION[a,b] FORMULATION NUMBER				
COMPONENTS	1	2	3	4	5
ALCOHOL					
N-Propanol[a]	70	-	-	-	70
Isopropyl[a]	-	70	-	-	-
Ethyl[a]	-	-	70	-	-
Mixtures					
N-Propanol[a]	-	-	-	50	-
Isopropyl[a]	-	-	-	20	-
FATTY ACIDS					
Emery 305[b]	2	2	2	2	-
Emery 644[b]	-	-	-	-	1
Glycerol monolaurate[b]	-	-	-	-	1.5
Polymers of fatty acids[b]	2	1	-	4	-

	CONCENTRATION[a,b] FORMULATION NUMBER				
COMPONENTS	1	2	3	4	5
DETERGENT					
Dodecylammonium chloride[b]	2	1	2	1	-
Hyamine 1622[b]	1	2	1	2	-
THICKENING AGENT					
Klucel[b] HFNF (1500-3000)	0.5	0.5	0.5	0.5	0.4
SCENTS					
Phenylethyl Alcohol[b]	0.25	0.25	0.25	0.25	2
Alpine Scent[b]	0.25	-	0.25	-	-
Baby Powder Scent[b]	-	0.25	-	0.25	-
PRESERVATIVE					
Zinc Omadine[b,c]	0.1	0.1	0.1	0.1	-
Liquipar Oil[b]	0.1	0.1	0.1	0.1	0.8

	CONCENTRATION[a,b] FORMULATION NUMBER				
COMPONENTS	1	2	3	4	5
ANTIOXIDANT					
Tenox PG[b]	-	-	-	-	0.1
Alpha tocopherol[b,d]	-	-	-	-	0.1
EMULSIFIER					
Polawax[b]	6	-	6	-	-
Arlacel[b]	-	3	-	3	-

[a] Concentration in percent (v/v).

[b] Concentration in percent (w/v).

[c] 48% suspension.

[d] 5IU/0.1 ml

liter distilled water with pH adjusted to 7.8) was added to each glove. All surfaces of the hand, especially areas around fingernails, were massaged for one minute. An aliquot of the sampling solution in each glove was then cultured for *Serratia marcescens* using standard microbiological techniques, and the changes in microbial count from baseline were obtained.

Results from the health care hand wash tests are given in Table VIII, where the data represent absolute colony counts. The baseline was a grand average of the three subjects and was 1 x 10^6 cfu/ml. Excellent antimicrobial action was indicated by a reduction in microbial count ranging from about 1 x 10^6 to about 60 cfu/ml after the first wash, to about 12.5 cfu/ml after the fifth wash, and to about 0 cfu/ml after the tenth wash.

Table VIII. ANTIMICROBIAL ACTION OF HEALTH CARE PERSONNEL HAND WASH ANTISEPTICS

	First Wash		Fifth Wash		Tenth Wash	
Subject	Left	Right	Left	Right	Left	Right
A	18	0	0	0	0	0
B	0	18	0	0	0	0
C	131	18	75	0	0	0

EXAMPLE 5: PREPARATION OF SURGICAL HAND SCRUB

To provide stronger cleansing action and deeper penetration of the antiseptic action preferred in pre-operative hand scrubbing, four formulations of surgical

hand scrubs were prepared by combining the ingredients given below in Table IX, adjusting the pH to 3.00-3.50 with phosphoric acid, and q.s. to 100 % with deionized water. The final concentrations are indicated either as percent (v/v) or percent (w/v).

EXAMPLE 6: QUANTITATIVE SKIN DEGERMING EVALUATION USING ENHANCED SKIN FLORA

Prior to surgery or any invasive procedure, the skin is initially prepped with antimicrobial products to reduce the quantity of microorganisms on the skin in order to prevent infections. This study was performed to study the effect of the novel antiseptic in its ability to reduce the flora of the skin as compared to a control site.

The Scrub formulation was prepared according to the procedure in Example 2, using the formulation in Table X, adjusting to pH 2.5 ± 0.5 with phosphoric acid, and q.s. to 100% with distilled water.

The Omadine cream was prepared according to the formulation in Table XI given in %(w/v), by melting the oil ingredients together at 40°C, adding the water phase ingredients to the oils while mixing, rewarming to 40°C, q.s. to 100% with distilled water, and allowing the mixture to congeal.

Following a minimum 6 day wash-out period, the backs of each of the volunteers were occluded with Saran Wrap and anchored with Leukosilk Dressing. Approximately forty-eight hours after occlusion the Saran Wrap was removed. The skin was allowed to air

Table IX. EXEMPLARY FORMULATIONS OF SURGICAL HAND SCRUB

	CONCENTRATION[a,b] FORMULATION NUMBER			
COMPONENTS	1	2	3	4
ALCOHOLS				
N-Propanol[a]	62	-	-	-
Isopropyl[a]	-	70	-	-
Mixtures				
(1) N-Propanol[a]	-	-	50	-
+ Isopropyl[a]	-	-	20	-
(2) N-Propanol[a]	-	-	-	40
+ Ethyl[a]	-	-	-	30
EMULSIFIER				
Polawax A31[b]	4	-	4	-
Arlacel 165[b]	-	4	-	4
DETERGENT				
Dodecylammonium chloride[b,c]	25	-	-	-
Amine Oxide[b]	-	10	-	-
Cetylpyridium chloride[b]	-	-	10	-
Hyamine 1622[b]	-	-	-	10
Mixtures				
Laurylamine oxide[b]	-	-	5	5
Dodecylammonium chloride[b]	-	10	5	5

COMPONENTS	CONCENTRATION[a,b] FORMULATION NUMBER 1	2	3	4
THICKENING AGENT				
Klucel[b] HFNF (1500-3000)	1	1	1	1
SCENTS				
Phenylethyl alcohol[b]	0.25	0.25	0.25	0.25
Alpine[b]	0.25	-	-	-
Other[b]	-	0.25	0.25	0.25
PRESERVATIVE				
Zinc Omadine[b,d]	2	1	2	1
Liquipar oil[b]	1	1	1	1
ANTIOXIDANT				
Tenox Pg[b]	0.10	-	0.10	-
Tenox S1[b]	-	0.10	-	0.10

[a] Concentration in percent (v/v).

[b] Concentration in percent (w/v).

[c] Hydro-alcoholic concentrate.

[d] 48% suspension.

Table X. FORMULATION FOR SURGICAL PREOPERATIVE ANTISEPTIC

COMPONENTS	CONCENTRATION[a,b]
N-Propanol[a]	70
Iodine crystals (I_2)[b]	2
Emery 644[b]	1
Klucel[b]	1
Tenox PG[b]	0.2
Sodium EDTA[b]	0.05
Glycerine[b]	2

[a] Concentration in percent (v/v).

[b] Concentration in percent (w/v).

Table XI. FORMULATION FOR OMADINE CREAM SURGICAL PREOPERATIVE ANTISEPTIC

COMPONENTS	CONCENTRATION[a]
OIL PHASE	
Stearyl alcohol[a]	4.53
Cetyl alcohol[a]	5.43
White petrolatum[a]	12.0
Mineral oil[a]	18.0
WATER PHASE	
Tween 80[a]	4.5
Sorbitol monolaurate[a]	2.0
Glycerine[a]	2.0
Aloe 10X[a]	2.0
Omadine[a]	1.5

[a] Concentration in percent (w/v).

dry. Then using a sterile template a grid was marked on the back with a sterile skin marker.

The Scrub Formulation was applied with a quarter of a sterile surgical sponge brush. The brush was immersed in the scrub solution and applied by rubbing the solution into the designated test area. The scrubbing with the brush continued for approximately 90 seconds, squeezing the brush as necessary to always assure that there was a generous amount of antiseptic present on the test site. After ninety-seconds, the brush was reimmersed in the solution and reapplied for another ninety-seconds. The scrub solution was applied for a total of 3.0 minutes. After the second

application the test site was allowed to completely dry by allowing the alcohol to evaporate.

The Omadine Cream was applied and rubbed into the skin for one minute by hand with the applicant wearing sterile gloves. The cream contained 1.5 % Omadine. Approximately five grams was applied to each test site.

Cultures were obtained using the quantitative culture scrub technique of Williams and Kligman, using a sterile scrubbing cup (5.07 cm^2, internal area) containing appropriate neutralizer sampling solution. Three milliliters of sampling solution is pipetted in and the area scrubbed with moderate pressure for one minute using a sterile Teflon "policeman". The fluid is aspirated, replaced with 3 ml of fresh solution, and the scrub is repeated. Cultures were obtained in this fashion at baseline, and at the following post-scrub times: ten minutes, six hours, and twenty-four hours.

Results of this study are presented in Table XII-XIV. Both antiseptic treatments provided reduction in microbial count as opposed to the control count. The alcohol-iodine antiseptic showed highly significant reduction within ten minutes of application and maintained the reduction over 24 hours, illustrating excellent quick-kill and persistence even in the absence of bispyrithione. The Zinc Omadine antiseptic showed significant decrease in microbial count at 10 minutes and indicated continued reduction over time.

Table XII. ALCOHOL ANTISEPTIC POST-TREATMENT MICROBIAL COUNT (LOG BASE 10 COUNTS/CM²)

Subject No.	Baseline	10 min.	6 Hours	24 Hours
# 1	5.982271	0.3802	0.38021	1.23045
# 2	0.857332	0.3802	0.38021	0.07918
# 3	5.301030	0.0792	0.07918	0.07918
# 4	6.079181	1.5051	0.07918	0.38021
# 5	5.079181	1.6127	1.98677	1.81291
# 6	5.612784	-	0.07918	0.07918
Mean	5.651963	0.6596	0.6433	0.61018
Log Reduction	-	4.9923	5.0086	5.04177

Table XIII. ZINC OMADINE POST-TREATMENT MICROBIAL COUNT (LOG BASE 10 COUNTS/CM²)

Subject No.	Baseline	10 min.	6 Hours	24 Hours
# 1	5.653213	5.6627	4.17609	2.98227
# 2	5.447158	5.7482	4.04139	2.81291
# 3	5.653212	5.0515	2.89763	3.07918
# 4	5.14973	4.7993	3.79239	3.07918
# 5	5.991226	5.7160	3,60206	3.62758
# 6	5.380211	4.8388	4.23044	3.14613
Mean	5.589999	5.3783	3.79000	3.12707
Log Reduction	-	0.21161	1.79999	2.46293

Table XIV. CONTROL AREA POST-TREATMENT MICROBIAL COUNT (LOG BASE 10 COUNTS/CM^2)

Subject No.	Baseline	10 min.	6 Hours	24 Hours
# 1	5.39794	5.9867	5.11394	5.04139
# 2	5.778151	5.8750	5.11394	5.07918
# 3	5.838849	5.7076	5.07918	5.14613
# 4	5.477121	6.5682	4.77085	4.94448
# 5	5.724276	6.2304	5.14612	5.56820
# 6	4.556303	4.9031	5.56820	4.61278
Mean	5.462107	5.8785	5.13204	5.065362
Log Reduction	-	0.4164	0.33065	0.396745

EXAMPLE 7: FORMULATION OF PREOPERATIVE ANTISEPTIC AND EVALUATION OF TREATMENT

Six formulations of preoperative antiseptics were prepared according to the procedure given in Example 2 by combining the ingredients given below in Table XV, adjusting the pH to 3.00-4.00 with phosphoric acid, and q.s. to 100 ml with deionized water. The final concentrations are indicated either as percent (v/v) or percent (w/v).

The antimicrobial action of the antiseptic Formulation #6 was compared to that of a soap and water scrub, and an Iodophor (Betadine) scrub, using the FDA patient preoperative skin preparation protocol which specifies the abdomen and groin crease as the test sites. *Federal Register* 59:31450-31452 (June 17, 1994). One contralateral side of the abdomen or groin crease

Table XV. FORMULATIONS OF PREOPERATIVE ANTISEPTICS

	CONCENTRATION[a,b] FORMULATION NUMBER					
COMPONENTS	1	2	3	4	5	6
ALCOHOL						
N-Propanol[a]	67	-	-	-	-	70
Isopropyl Alcohol[a]	-	70	-	-	-	-
Ethyl Alcohol[a]	-	-	70	-	-	-
Mixtures						
N-Propanol[a]	-	-	-	40	-	-
+ Isopropyl[a]	-	-	-	30	-	-
N-Propanol[a]	-	-	-	-	50	-
+ Amyl[a]	-	-	-	-	17	-
PROPYLENE GLYCOL[a]	5	-	-	-	-	-
EMULSIFIER						
Polawax[b]	6	6	6	6	6	6

COMPONENTS	CONCENTRATION[a,b] FORMULATION NUMBER 1	2	3	4	5	6
FATTY ACIDS						
Emery 644[b]	2	-	2	-	2	2
Emery 305[b]	-	2	-	2	-	-
NITROGEN COMPOUND						
Dodecylammonium chloride[b,c]	4	-	-	-	4	-
Hyamine 1622[b]	-	2	-	-	-	2
Laurylamine oxide[b]	-	-	2	-	-	-
Cetylpyridium chloride[b]	-	-	-	2	-	-
OTHER QUICK-KILL AGENT						
Chlorhexidine[b]	-	1	-	-	-	-
Triclosan[b]	-	-	1	-	-	-
PCMX[b,e]	-	-	-	1	-	-
Iodine[b]	-	-	-	-	2	-
+ Sodium iodide[b]	-	-	-	-	4	-
PRESERVATIVE						
Zinc Omadine[b,d]	2	2	2	2	-	2
Liquipar Oil[b]	-	-	-	-	1	-

COMPONENTS	CONCENTRATION[a,b] FORMULATION NUMBER 1	2	3	4	5	6
AROMATIC ALCOHOL						
Phenylethyl alcohol[b]	0.25	-	0.25	-	0.25	0.25
Benzyl alcohol[b]	-	4	-	4	-	-
ANTIOXIDANT						
Tenox PG[b]	0.1	-	0.1	-	0.1	0.1
Tenox S1[b]	-	0.1	-	0.1	-	-

[a] Concentration in percent (v/v).

[b] Concentration in percent (w/v).

[c] Hydro-alcoholic concentrate.

[d] 48% suspension.

[e] PCMX = para-chloro-meta-zylenol

is used as the test site and the other side was used as the baseline control site. Samples were taken at baseline and then at 10 minutes, 6 hours, and 24 hours posttreatment, using the scrubbing cup technique described in Example 6. The scrub time for the antiseptic Scrub formulation and soap and water was three minutes, and the Iodophor was five minutes.

The results from the comparative study (Table XVI-XXI) show that at all time points, the antimicrobial action of the antiseptic was higher than with soap and water, and with iodophor. At ten minutes posttreatment with the antiseptic, there was 59-100% drop in organism count for the abdomen and 87-100% drop for the groin crease, demonstrating very effective quick-kill. Overall, 48-100% drop in organism counts were maintained through twenty-four hours posttreatment with the antiseptic.

EXAMPLE 8: PREPARATION OF ACNE TREATMENT ANTISEPTIC AND EVALUATION OF ACNE TREATMENT

Cream formulations of the antiseptic solution given in Table XXII and XXIII were prepared according to the following procedure. Water and water soluble ingredients were combined and heated to 75-80°C with agitation. The lipids and lipid soluble ingredients were combined and heated to 75°C with agitation. The water soluble portion and the lipid soluble portion were combined cooled to 50°C with agitation. A buffer and preservative were added followed by q.s. to 100 ml with deionized water, and the resulting cream was cooled to

Table XVI. LOG10 CHANGES IN COUNTS FROM BASELINE
WITH THREE MINUTE SCRUB WITH ANTISEPTIC
SITE: ABDOMEN

Subject	Base line	10 min	Log Drop	% Drop	6 Hr	Log Drop	% Drop	24 Hr	Log Drop	% Drop
A	1.3324	0.0000	1.3324	100.00	0.0000	1.3324	100.00	0.0000	1.3324	100.00
B	2.9138	0.6021	2.3118	79.34	0.0000	2.9138	100.00	0.3979	2.5158	86.34
C	DATA	NOT	DONE							
D	1.6767	0.0000	1.6767	100.00	-0.3010	1.9777	117.95	-0.3010	1.9777	117.95
E	2.2695	0.0000	2.2695	100.00	-0.3010	2.5705	113.26	0.0000	2.2695	100.00
F	1.8388	0.0000	1.8388	100.00	0.9777	0.8611	46.83	0.0000	1.8388	100.00
G	2.2455	0.9294	1.3161	58.61	0.0000	2.2455	100.00	0.0000	2.2455	100.00
H	1.2304	0.0000	1.2304	100.00	0.0000	1.2304	100.00	-0.3010	1.5315	124.47
MEAN	1.9296	0.2187	1.7108	91.14	0.0537	1.8759	96.86	-0.0292	1.9588	104.11

Table XVII. LOG10 CHANGES IN COUNTS FROM BASELINE

WITH THREE MINUTE SCRUB WITH ANTISEPTIC

SITE: GROIN CREASE

Subject	Base-line	10 min.	Log Drop	% Drop	6 Hr	Log Drop	% Drop	24 Hr	Log Drop	% Drop
A	4.2516	0.5441	3.7076	87.20	0.0000	4.2516	100.00	0.0000	4.2516	100.00
B	3.5740	0.0000	3.5740	100.00	0.0000	3.5740	100.00	1.8722	1.7019	47.62
C	DATA	NOT	DONE							
D	4.2214	0.0000	4.2214	100.00	1.6902	2.5312	59.96	2.0191	2.2023	52.17
E	2.6385	0.0000	2.6385	100.00	0.3010	2.3375	88.59	0.0000	2.6385	100.00
F	5.2292	0.0000	5.2292	100.00	1.0969	4.1323	79.02	0.3979	4.8312	92.39
G	3.6335	0.0000	3.6335	100.00	0.3010	3.3324	91.72	0.0000	3.6335	100.00
H	5.0394	0.0000	5.0394	100.00	0.8751	4.1644	82.64	-0.3010	5.3404	105.97
MEAN	4.0840	0.0777	4.0062	98.17	0.6092	3.4748	85.99	0.5697	3.5142	85.45

Table XVIII. LOG10 CHANGES IN COUNTS FROM BASELINE
WITH THREE MINUTE SCRUB WITH SOAP/WATER
SITE: ABDOMEN

Subject	Baseline	10 min	Log Drop	% Drop	6 Hr	Log Drop	% Drop	24 Hr	Log Drop	% Drop
A	0.0000	0.5441	-0.5441	00.00	0.0000	0.0000	00.00	-0.3010	0.3010	00.00
B	1.4771	0.6021	0.8751	59.24	0.7782	0.6990	47.32	0.3010	1.1761	79.62
C	DATA	NOT	DONE							
D	2.1569	1.4914	0.6655	30.85	1.1761	0.9818	45.47	1.2175	0.9394	43.55
E	2.1106	0.6532	1.4574	69.05	0.8451	1.2655	59.96	1.4698	0.6408	30.36
F	2.1973	2.6532	-0.4559	-20.75	0.3010	1.8963	86.30	2.1383	0.0590	2.68
G	1.0607	-0.3010	1.3617	128.38	0.4771	0.5836	55.02	0.0000	1.0607	100.00
H	3.9345	1.7443	2.1902	55.67	0.8751	3.0594	77.76	0.3979	3.5366	89.89
MEAN	1.8482	1.0553	0.7928	46.06	0.6361	1.2121	53.12	0.7462	1.1019	49.44

Table XIX. LOG10 CHANGES IN COUNTS FROM BASELINE

WITH THREE MINUTE SCRUB WITH SOAP/WATER

SITE: GROIN CREASE

Subject	Baseline	10 Min	Log Drop	% Drop	6 Hours	Log Drop	% Drop	24 Hours	Log Drop	% Drop
A	0.0000	2.7482	-2.7482	00.00	1.3010-	-1.3010	0.000	0.6990	-0.6990	0.00
B	2.6284	2.7818	-0.1534	-05.83	2.6233	0.0051	0.200	2.1903	0.4381	16.67
C	DATA	NOT	DONE							
D	5.2055	5.0512	0.1543	02.96	3.7076	1.4979	28.78	3.8543	1.3512	25.96
E	3.1239	2.6181	0.5058	16.19	1.8751	1.2488	39.98	2.1903	0.9335	29.88
F	5.1658	4.3493	0.8166	15.81	4.3909	0.7749	15.00	3.9800	1.1858	22.97
G	4.2822	2.8325	1.4497	33.85	2.6284	1.6538	36.62	1.3010	2.9811	69.62
H	4.5447	1.2787	3.2659	71.86	2.8692	1.6755	36.87	1.8451	2.6996	59.40
MEAN	3.5643	3.0942	0.4701	19.26	2.7708	0.7936	22.78	2.2943	1.2701	32.07

Table XX. LOG10 CHANGES IN COUNTS FROM BASELINE

WITH FIVE MINUTE SCRUB WITH IODOPHOR

SITE: ABDOMEN

Subject	Baseline	10 Min	Log Drop	% Drop	6 Hours	Log Drop	% Drop	24 Hours	Log Drop	% Drop
I	0.9031	0.0000	0.9031	100.00	1.6021	-0.6990	-77.40	0.0000	0.9031	100.00
J	1.0792	0.1761	0.9031	83.68	0.0000	1.0792	100.00	1.1761	-0.0969	-8.98
K	2.6335	2.0128	0.6206	23.57	2.3222	0.3113	11.62	1.5882	1.0065	40.45
L	1.3979	0.7404	0.6577	47.04	1.6532	-0.2553	-18.26	0.0000	1.3979	100.00
M	1.3324	2.7076	-1.3751	-103.20	0.6990	0.6335	47.54	1.3010	0.0314	2.35
N	DATA	NOT	DONE							
O	2.4624	1.1761	1.2863	52.24	2.5682	-0.1058	- 4.30	1.8451	0.6173	25.07
P	DATA	NOT	DONE							
MEAN	1.6348	1.1355	0.4993	33.89	1.4741	0.1606	9.90	0.9817	0.6530	43.15

Table XXI. LOG10 CHANGES IN COUNTS FROM BASELINE

WITH FIVE MINUTE SCRUB WITH IODOPHOR

SITE: GROIN CREASE

Subject	Baseline	10 Min.	Log Drop	% Drop	6 Hours	Log Drop	% Drop	24 Hours	Log Drop	% Drop
I	5.4166	4.3086	1.1081	20.46	1.5441	3.8726	71.49	0.0000	5.4166	100.00
J	3.1055	1.0212	2.0843	67.12	1.3979	1.7076	54.99	1.5441	1.5614	50.28
K	5.6154	3.9978	1.6178	28.81	2.7672	2.8483	50.72	2.6233	2.9922	53.28
L	3.2122	0.0000	3.2122	100.00	3.3365	-0.1243	-3.87	1.1761	2.0361	63.39
M	3.2765	3.1207	0.1559	4.76	2.1903	1.0861	33.15	1.0000	2.2765	59.48
N	DATA	NOT	DONE							
O	5.0683	3.4914	1.5750	31.09	3.1156	1.9507	38.50	3.7443	1.3220	28.09
P	DATA	NOT	DONE							
MEAN	4.2821	2.6566	1.6255	42.04	2.3919	1.8912	42.83	1.6813	1.6008	60.42

Table XXII. EXEMPLARY FORMULATIONS OF THE ACNE CREAMS

	CONCENTRATION[a]				
	FORMULATION NUMBER				
COMPONENTS	1	2	3	4	5
OILS					
Emersol 305[a]	5	10	5	10	2
Mineral oil[a]	5	-	-	-	10
Safflower oil[a]	5	5	5	-	-
Wheat germ oil[a]	3	3	3	8	-
Stearyl alcohol[a]	-	-	-	-	5.5
Cetyl alcohol[a]	-	-	-	-	4.7
EMULSIFIER					
Polawax[a]	10	10	10	10	-
Sodium lauryl sulfate[a]	-	-	-	-	1.5
PENETRATION INHIBITOR					
White petrolatum[a]	10	10	10	10	12.5
ANTIOXIDANT					
Tenox S1[a]	10	10	10	10	5
+ Propylene glycol[b]	7	7	7	7	-
+ Propyl gallate[a]	2	2	2	2	-
+ Citric acid[a]	1	1	1	1	-
Tenox Pg[a]	2	2	2	2	-
PRESERVATIVE					
Zinc Omadine[a,c]	1.5	1.5	1.5	1.5	1.5

	CONCENTRATION[a] FORMULATION NUMBER				
COMPONENTS	1	2	3	4	5
KERATOLYTIC AGENT					
Salicylic acid[a]	0.5	-	-	-	-
Resorcinol[a]	-	5	-	3	-
Resorcinol monoacetate[a]	-	-	5	-	-
Sulfur[a]	-	-	-	3	-
ANTIBIOTIC					
Erythromycin[a]	-	2	-	-	-
Clindamycin[a]	-	-	2	-	-
Tetracycline[a]	-	-	-	2	-

[a] Concentration in weight percent (w/v).

[b] Inhibits penetration beyond the basal cell layer.

[c] 48% suspension.

Table XXIII. EXEMPLARY FORMULATIONS OF CYSTIC ACNE FORMULAE

COMPONENTS	CONCENTRATION[a,b]
ALCOHOL	
Decanol[a]	2%
FATTY ACIDS	
Emersol 305[b]	2%
PRESERVATIVE	
Zinc Omadine[b]	2%
PENETRATING AGENT	
Propylene Glycol[a]	10%
ANTIOXIDANT	
Propyl Gallate[b]	1%
ADDITIONAL ADDITIVES	
Progesterone[b]	0.50%
Aldactone[b]	1%

[a] Concentration in volume percent (v/v).

[b] Concentration in weight percent (w/v).

[c] The above ingredients may be mixed with short-chain alkyl alcohols or mixed in a cream base without medium-chain alcohols which would inhibit penetration.

25°C with agitation. In formulas that contain Zinc Omadine, the cream was cooled before adding the Zinc Omadine.

Three hundred patients with acne were referred to a board certified dermatologist for treatment with Formulation #5 in Table XXII for patients suffering

from inflammatory, papular, and papulopustular acne and with the formulation in Table XXIII, for cystic acne. All of these patients had failed oral antibiotic therapy for acne. The patients with inflammatory, papular and papulopustular had dramatic improvement with resolution of their acne in 50% of the cases and great improvement in 25% of the cases. Approximately 25% of the cases only had mild improvement. In patients showing only mild improvement, Retin A was added to their treatment regimen for two weeks with resolution of their recalcitrant acne. Retin A was used at bedtime, and the acne antiseptic cream was used in the morning on patients suffering from primary follicular obstruction. After about two weeks of this combination therapy the patients were able to stop Retin A but continue the acne cream with control of their acne. The acne antiseptic cream helped reduce the inflammatory response normally seen with Retin A.

For treatment of cystic acne, the dermatologist's impression was that the formulation given in Table XXIII was better than the prescription medication benzamycin (a combination of erythromycin and benzoyl peroxide in a alcohol base).

In the treatment of acne there did not seem to be any difference in response to where the patient was afflicted, i.e., face, anterior chest or back. The incidence of side-effects were less than one percent and restricted to a mild stinging sensation initially when the cream was applied. In patients only receiving the novel acne formulation the patients were instructed

to rub in a small amount of cream to the face prior to bedtime, i.e., once a day treatment.

EXAMPLE 9: TREATMENT OF ACNE ROSACEA WITH ACNE CREAM

Ten patients with acne rosacea resistant to improvement with metronidazole cream and antibiotics were treated with Formulation #5 in Table XXII. All patients had complete resolution of the inflammation of acne rosacea. All patients were able to discontinue their metronidazole and antibiotics. If Emery 644 was substituted for Emersol 305 all of the patients became much worse. If the patient discontinued the acne rosacea cream they had recrudescence of their acne rosacea after about seven to ten days. When the acne rosacea cream was reapplied once a day at bedtime there was again complete healing of their acne rosacea in about seven to fourteen days.

EXAMPLE 10: PREPARATION OF PSORIASIS AND SEBORRHEA CREAM AND EVALUATION OF TREATMENT

Antiseptic creams for treatment of psoriasis and seborrhea were prepared as given in Table XXIV for Formulation #5 and #6, respectively.

Twenty patients with primary seborrhea of the face and neck were treated with one of the acne formulations in a cream base. The patients suffered from scaly, flaky skin of the eyebrows, naso-labial folds and sometimes post-auricular areas. The cream formulation could be applied once a day with resolution of the seborrhea in all cases.

Table XXIV. EXEMPLARY FORMULATIONS OF PSORIASIS AND SEBORRHEA ANTISEPTIC TREATMENT

	CONCENTRATION[a] FORMULATION NUMBER					
COMPONENTS	1	2	3	4	5	6
OILS						
Emersol 305[a]	15	10	15	10	10	2
Mineral oil[a,b]	5	-	-	5	10	10
Safflower oil[a,b]	5	5	5	-	-	-
Wheat germ oil[a,b]	3	3	3	8	-	-
Stearyl alcohol[a]	-	-	-	-	5.5	5.5
Cetyl alcohol[a]	-	-	-	-	4.7	4.7
PENETRATION INHIBITOR						
White petrolatum[a,b]	10	10	10	10	12.5	12.5
EMULSIFIER						
Polawax[a]	10	-	10	-	-	-
Glyceryl monostearate[a]	-	2	-	2	-	-
Sodium lauryl sulfate[a]	-	-	-	-	1.5	1.5
ANTIOXIDANT						
Tenox S1[a]	20	20	20	20	5	5
Tenox PG[a]	3	3	3	3	-	-
PRESERVATIVE						
Zinc Omadine[a,c]	2.5	2.5	2.5	2.5	1.5	1.5
ADDITIONAL INGREDIENTS						
Coal tar[a]	0.5	1.0	0.5	1.0	-	-
LCD[a]	1.5	-	-	1.0	-	-

[a] Concentration in weight percent (w/v).

[b] Inhibits penetration beyond the basal cell layer.

[c] 48% suspension.

Ten patients with mild to moderate psoriasis of the elbows, knees, and gluteal area were treated with a cream formulation containing Zinc Omadine, GLA 70 (purified gamma dihomo-linoleic acid), and Emersol 305. These patients are slow to respond, usually taking seven to ten days to show moderate improvement and full resolution in about twenty days. There were no failures in treatment of psoriasis. The patients had more rapid improvement if the medication was applied twice a day rather than once a day.

EXAMPLE 11: PREPARATION OF ANTIFUNGAL CREAM AND EVALUATION OF TREATMENT OF ONYCHOMYCOSIS, ATHLETE'S FOOT AND TINEA VERSICOLOR

Antifungal antiseptic creams were prepared according to the procedure in Example 8, using the formulations given in Table XXV.

Six patients with onychomycosis of either the fingernails or toenails were treated with Formulation #5 of the antiseptic given in Table XXV. They were instructed to rub in the cream at the base of the afflicted nail once a day. Some patients also would apply the cream with a blunt instrument under the nail. All patients had resolution of their onychomycosis, growing in a clean, noninfected nail from the base. The treatment was prolonged due to the time required to grow a new nail but was effective in all cases.

Ten patients suffering from tinea pedis (athlete's foot) who had failed treatment with tinactin after four to six weeks were treated with Formulation #5 in Table

Table XXV. EXEMPLARY FORMULATIONS OF ANTIFUNGAL CREAM

	CONCENTRATION[a] FORMULATION NUMBER					
COMPONENTS	1	2	3	4	5	6
OILS						
Emersol 305[a]	5	10	5	10	2	2
Mineral oil[a]	5	-	-	-	10	10
Safflower oil[a]	5	5	5	-	-	-
Wheat germ oil[a]	3	3	3	8	-	-
Stearyl alcohol[a]	-	-	-	-	5.5	5.5
Cetyl alcohol[a]	-	-	-	-	4.7	4.7
FATTY ACIDS						
Acetic Acid[a]	2	-	-	-	-	-
Propionic Acid[a]	-	2	-	-	-	-
Emery 658[a]	-	-	2	-	-	-
Lauric Acid[a]	-	-	-	2	-	-
PENETRATION INHIBITOR						
White petrolatum[a,c]	10	10	10	10	12.5	12.5
EMULSIFIER						
Polawax[a]	10	-	10	-	-	-
Glyceryl monostearate[a]	-	2	-	2	-	-
Sodium lauryl sulfate[a]	-	-	-	-	1.5	1.5
ANTIOXIDANT						
Tenox S1[a]	10	10	10	10	5	5
Tenox PG[a]	2	2	2	2	-	-

COMPONENTS	CONCENTRATION[a] FORMULATION NUMBER 1	2	3	4	5	6
PRESERVATIVE						
Zinc Omadine[a,d]	1.5	1.5	1.5	1.5	1.5	1.5
PROPYLENE GLYCOL[b]	-	-	-	-	-	70
ANTIBIOTICS						
Undecylenic Acid[a]	-	1	-	-	-	-
Miconazole[a]	-	-	2	-	-	-
Clotrimazole[a]	-	-	-	2	-	-

[a] Concentration in weight percent (w/v).

[b] Concentration in volume percent (v/v).

[c] Inhibits penetration beyond the basal cell layer.

[d] 48% suspension.

XXV. The patients were given a formula depending upon the type of athlete's foot they suffered. Some patients had the wet, soggy type of athlete's foot, whereas other patients had "moccasin foot". The patients with the wet, soggy type were given astringents using aluminum acetate and glacial acetic acid (Burrow's solution) or aluminum chloride hexahydrate at a 5%-15% concentration. The patients with the dry type of athlete's foot were treated with cream formulations. All patients had resolution of their tinea pedis within seven to ten days.

One dozen patients with tinea versicolor of the anterior chest, shoulders and arms were treated with Formulation #6 in Table XXV. These patients were able

to use the medicine once a day at bedtime with complete resolution of their infection with *Malassazia furfur* within two weeks.

EXAMPLE 12: PREPARATION OF WOUND AND BURN CARE ANTISEPTIC AND EVALUATION OF TREATMENT

Wound and burn care antiseptic formulae were prepared according to the procedure in Example 2, using the formulation in Table XXVI, q.s. to 100% with propylene glycol.

Table XXVI. FORMULATION OF WOUND AND BURN CARE ANTISEPTIC

COMPONENTS	CONCENTRATION
FATTY ACID	
Emery 305	4.00 ml
PRESERVATIVE	
Propionic acid	4.00 ml
Omadine disulfide	0.10 grams
pH ADJUSTING AGENT	
Dequest 2010	1.00 ml
THICKENING AGENT	
Klucel	0.50 grams
ADDITIONAL INGREDIENTS	
Lidocaine	2.00 grams
Hyaluronic acid (Sodium Salt)	120 μg/ml

Four patients with peri-rectal lesions that failed to heal for three months to three years following either total colectomy or pilo-nidal cyst surgery were treated with the wound care formulation twice a day. The patients soaked the antiseptic formulation in sterile gauze and packed the area twice a day. All patients had complete healing of their infected abscesses within ten to fourteen days.

One patient was treated with the wound care formula for second and third degree burns of the face, shoulder, side and thigh. Sterile gauze was saturated with the antiseptic formula and wrapped over the area two to three times a day. The burns healed completely without infection or scar formation.

EXAMPLE 13: PREPARATION OF ANTISEPTIC EYE TREATMENT AND EVALUATION OF TREATMENT

Antiseptic eye treatment was prepared according to the procedure in Example 1, using the formulation in Table XXVII.

The treatment of both bacterial and viral eye infections has been accomplished using 5% propionic acid, 1%-5% zinc sulfate, and with either Omadine MDS or Omadine DS at 0.1% as the preservative. This formulation is applied every four hours with rapid resolution of both viral or bacterial eye infections.

Table XXVII. EXEMPLARY FORMULATIONS OF ANTISEPTIC EYE TREATMENT

COMPONENTS	CONCENTRATION[a,b]
PROPYLENE GLYCOL[a]	85%
FATTY ACIDS	
Propionic Acid[b]	5%
Emery 658[b]	0.1%
Emery 305[b]	0.1%
PRESERVATIVE	
Zinc Omadine[b]	0.1%
ADDITIONAL INGREDIENTS	
Sodium EDTA[b]	1.0%
Deionized Water[a]	6.7%
Electrolytes[c]	
OPTIONAL INGREDIENT	
Zinc sulfate[b]	1.0%

[a] Concentration in percent volume (v/v).

[b] Concentration in weight percent (w/v).

[c] Concentration of electrolytes to make formulation isotonic and to buffer to pH 5.0

EXAMPLE 14: PREPARATION OF CANINE EAR ANTISEPTIC DROPS AND EVALUATION OF TREATMENT OF EXTERNAL OTITIS

Canine ear antiseptic drops were prepared according to the procedure in Example 2, using the formulation in Table XXVIII.

Thirty dogs with primary acute external otitis due to a mixture of gram negative and gram positive organisms were treated with the external otitis

Table XXVIII. EXEMPLARY FORMULATIONS OF CANINE EAR ANTISEPTIC DROPS

COMPONENTS	CONCENTRATION[a,b]
PROPYLENE GLYCOL[a]	60%
FATTY ACIDS	
Emersol 305	10 ml
EMULSIFIER	
Polawax	6.66 grams
PRESERVATIVE	
Zinc Omadine[b]	7.12 ml
THICKENING AGENT	
Klucel	0.25 grams
AROMATIC ALCOHOL	
Phenylethyl alcohol	6.66 ml
pH ADJUSTING AGENT	
Glacial acetic acid[c]	29.3 ml
ADDITIONAL INGREDIENTS	
Aluminum acetate	33.3 grams
Lidocaine base	5.19 grams
Betamethasone	666 mg
DEIONIZED WATER	q.s. to 333.33 ml

[a] Concentration in percent volume (v/v).

[b] 48% suspension

[c] Final product has a pH between 3.5 and 4.5.

formula. The medication was applied twice a day. There was complete resolution of the otitis in all cases without overgrowth of the fungus, *Malassia canis*. This formulation is very effective against the normal pathogens, e.g., *Pseudomonas* sp. and staphylococci occurring in both dogs and humans. Also, the formulation is very effective against *Aspergillus sp.*

EXAMPLE 15: PREPARATION OF ANTIBIOTIC CREAM

Antibiotic creams were prepared according to the procedure in Example 8, using the formulations in Table XXIX.

EXAMPLE 16: PREPARATION OF MUCOUS MEMBRANE ANTISEPTIC

Mucous membrane antiseptics were prepared according to the procedure in Example 2, using the formulations in Table XXX, adjusting the pH to 4 and q.s. to 100 ml with deionized water.

EXAMPLE 17: PREPARATION OF HERPES TREATMENT AND EVALUATION OF TREATMENT

Antiseptic for the treatment of herpes virus was prepared according to the procedure in Example 2, using the formulations given in Table XXXI.

Twenty patients with recurrent orolabial Herpes simplex were treated with one of the formulations given in Table XXXI, each containing a membrane partitioning formula of long-chain fatty acids, zinc sulfate and methyl and propyl esters of gallic acid. The patients were instructed to apply the formulation with a cotton

Table XXIX. EXEMPLARY FORMULATIONS OF ANTIBIOTIC CREAM

	CONCENTRATION[a] FORMULATION NUMBER			
COMPONENTS	1	2	3	4
OILS				
Mineral oil	5	-	-	-
Safflower oil	5	5	5	-
Wheat germ oil	3	3	3	8
FATTY ACID				
Emersol 305	5	10	5	10
PENETRATION INHIBITOR[b]				
White petrolatum	10	10	10	10
EMULSIFIER				
Polawax	10	-	10	-
Glyceryl monostearate	-	2	-	2
ANTIOXIDANT				
Tenox S1	10	10	10	10
Tenox PG	2	2	2	2
PRESERVATIVE				
Zinc Omadine[c]	1.5	1.5	1.5	1.5
ANTIBIOTICS				
Neosporin	1	-	-	-
Chloramphenicol	-	1	-	-
Tetracycline	-	-	2	-
Gentamicin	-	-	-	1
DEIONIZED WATER	q.s. to 100 ml			

[a] Concentration in weight percent (w/v).

[b] Inhibits penetration beyond basal cell layer.

[c] 48% suspension.

Table XXX. EXEMPLARY FORMULATIONS OF MUCOUS MEMBRANE ANTISEPTIC

	CONCENTRATION[a,b] FORMULATION NUMBER				
COMPONENTS	1	2	3	4	5
PROPYLENE GLYCOL[a]	60	60	60	60	60
ANTIOXIDANT					
Tenox S1[b]	10	10	10	10	10
EMULSIFIER					
Polawax[b]	6	6	6	6	6
FATTY ACIDS					
Emery 644[b]	12	-	7	-	7
Emery 305[b]	-	10	-	2	-
Glacial Acetic Acid[b]	5	-	-	5	5
Propionic Acid[b]	-	5	5	-	-
Glycerol Monolaurate[b]	-	-	-	-	3
Emery 658[b]	-	5	1	4	2
PRESERVATIVE					
Zinc Omadine[b,c]	1	1	1	1	1
THICKENING AGENT					
Klucel[b] HFNF - 1500-3000	0.5	0.5	0.5	0.5	0.5
AROMATIC ALCOHOL					
Phenylethyl alcohol[b]	1	1	1	1	1
CHELATOR					
Dequest 2010 and 2060[b]	1	1	1	1	1
pH ADJUSTING AGENT[b]					
Sodium acetate or sodium propionate	adjust pH to 4.0				

[a] Concentration in percent volume (v/v).

[b] Concentration in weight percent (w/v).

[c] 48% suspension

Table XXXI. EXEMPLARY FORMULATIONS OF HERPES TREATMENT

	CONCENTRATION[a,b] FORMULATION NUMBER			
COMPONENTS	1	2	3	4
PROPYLENE GLYCOL[a]	35	35	35	35
ALCOHOLS				
Decanol[a]	10	25	25	25
Ethyl alcohol[a]	29	12	10	12
FATTY ACIDS				
Emery 305[b]	8	8	8	8
Lauric Acid[b]	-	4	7	2
Emery 658[b]	7	3	-	2
Glycerol monolaurate[b]	-	-	-	3
GALLIC ACID ESTERS				
Propyl gallate[b]	3	3	3	3
Methyl gallate[b]	3	3	3	3
ADDITIONAL INGREDIENTS				
Amine oxide[b]	-	2	4	2
Lidocaine[b]	5	5	5	5
Zinc sulfate[b]	0.5 - 5.0%	2.5 ml of glycerin		

[a] Concentration in percent volume (v/v).

[b] Concentration in weight percent (w/v).

ball saturated with the anti-viral solution during the prodrome phase of their illness every six hours. Several patients (about half) would have complete ablation of their herpes, with prevention of further progression of their herpes, including ulceration lesions they would normally experience. The other half

of the patients would progress to develop an ulcerated lesion which was smaller than their usual lesions and would heal in about two to three days rather than the usual seven to ten days.

EXAMPLE 18: PREPARATION OF BURN TREATMENT

Antiseptic for burn treatment was prepared by combining linoleic acid with or without silver sulfadiazine, and phenethylamine (PEA) in a cream vehicle or lotion.

EXAMPLE 19: PREPARATION OF A MUCOADHESIVE TREATMENT

An antiseptic mucoadhesive treatment to be used as a urethral gel or in treatment of aphthous ulcers was prepared according to the procedure below, using the formulations in Table XXXII. The liquid and cream compositions were prepared by heating with stirring the polyethylene glycol fractions with the long chain unsaturated fatty acids and alcohols with heating and stirring these components to about 65°-70°C, at which temperature any solid or semi-solid polyethylene glycols present were liquefied and formed a fraction of syrupy, gel-like consistency. The sodium carboxymethyl- cellulose and poly(ethylene oxide) homopolymer constituents of the polymeric adhesive component were mixed together thoroughly and added to the polyethylene glycol and long-chain unsaturated fatty acids and alcohol fractions, slightly cooled to about 50°-60°C, with constant stirring to obtain a uniform mixture. The mixture was cooled to about or

Table XXXII. EXEMPLARY FORMULATIONS OF MUCOADHESIVE TREATMENT

	CONCENTRATION[a,b] FORMULATION NUMBER		
COMPONENTS	1	2	3
POLYETHYLENE GLYCOL[a]			
600	18	-	-
400	36	55	44
8000	1.5	2.3	2.8
SODIUM CARBOXYMETHYL-CELLULOSE (CMC 7H3S)[b]	30.0	24	37.5
POLYETHYLENE OXIDE[b] HOMOPOLYMER (Polyox WSR-301)	10.0	8	12.5
FATTY ACIDS			
Emery 644[b]	2	-	2.6
Emery 305[b]	-	2.5	5
AROMATIC ALCOHOL			
Phenylethyl Alcohol[b]	-	1.5	2
PRESERVATIVE			
Omadine[b]	0.4	0.5	0.1
GALLIC ACID ESTERS			
Propyl gallate[b]	0.1	0.2	-
Methyl gallate[b]	1.0	1.0	-
Beta-hydroxytoluene[b]	-	-	0.5
ADDITIONAL INGREDIENTS			
Lidocaine[b]	1	5	1

[a] Concentration in percent volume (v/v).

[b] Concentration in weight percent (w/v).

slightly below 40°C before addition of the phenylethyl alcohol and Zinc Omadine.

EXAMPLE 20: APPLICATION OF *PSEUDOMONAS* TO INTACT SKIN FOLLOWED BY APPLICATION OF NOVEL ANTISEPTIC

An overnight culture of *Pseudomonas aeruginosa* containing 4.09×10^8 was obtained. A tenth of a ml. (0.1 ml) of this culture was applied to the intact forearm skin of three healthy volunteers. The count/square inch applied was 1.82×10^7. The *Pseudomonas* was allowed to air-dry for ten minutes. The antiseptic given as Formulation #5 in Table VII was applied to the site for one minute and allowed to air-dry. Cultures were obtained of the antiseptic treatment site and control sites one hour later, and are presented in Table XXXIII.

Table XXXIII. MICROBIAL COUNTS OF *Pseudomonas*/IN^2 AFTER APPLICATION OF ANTISEPTIC

	Subject # 1		Subject # 2		Subject # 3	
	Right	Left	Right	Left	Right	Left
Test Gel	0	9.5	0	0	17	0
Initial Control	1.71×10^6		9.3×10^6		1.16×10^6	
Control count at 1 hour	5.00×10^4		4.5×10^4		5.00×10^4	

EXAMPLE 21: PREPARATION OF ANTISEPTIC TEAT DIP

Bovine mastitis is a continuing problem with dairy herds despite the use of antiseptic teat dips. A novel formulation was prepared using the novel ingredients of the antiseptic with ingredients from the GRAS (Generally Recognized As Safe) list of the Food and Drug Administration. Especially important are linoleic and linolenic fatty acids as these form a lipid coat on the external surface and distal portions of the teat canal.

EXAMPLE 22: PREPARATION OF DODECYLAMMONIUM CHLORIDE/HYDRO-ALCOHOLIC CONCENTRATE

Dodecylammonium chloride hydro-alcoholic concentrate was prepared by combining the following:

Dodecylamine	100.00 grams
37% conc. HCL	53.19 grams
Deionized Water	56.24 grams
N-Propanol	89.75 grams
Total	299.18 grams